VOLUME 1 • AUGUST 1959 • NUMBER 2

A.M.A. ARCHIVES OF

NEUROLOGY

Studies in Alcoholism
Joseph Schiller, Robert E. Peck, and Moe A. Goldberg

Familial Spastic Paraplegia with Amyotrophy, Oligophrenia, and Central Retinal Degeneration
Kage Kjellin

Experimental Focal Epilepsy in Animals
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Archives of Neurology

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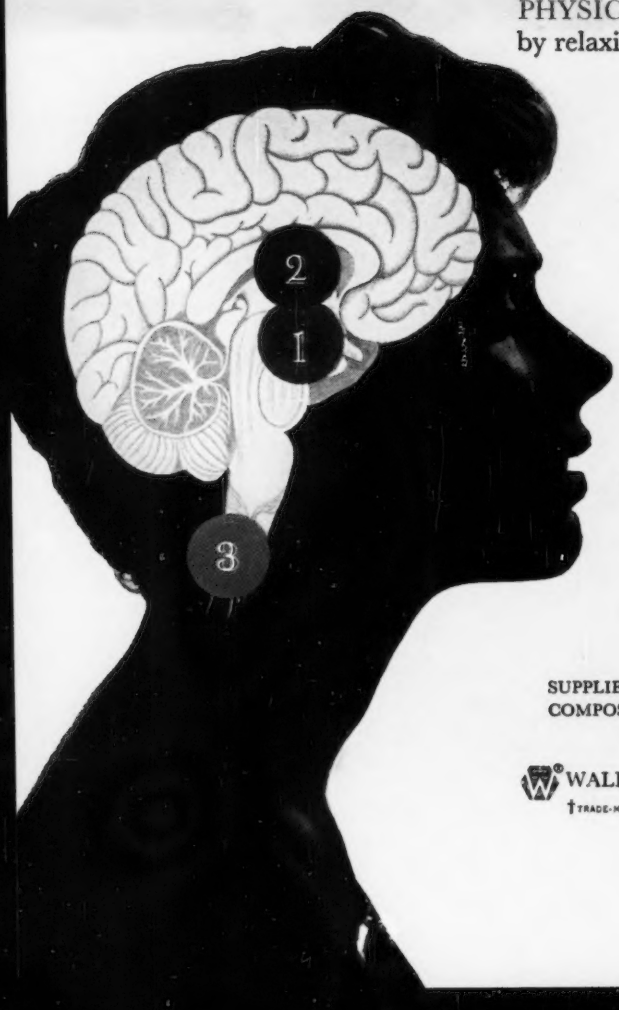

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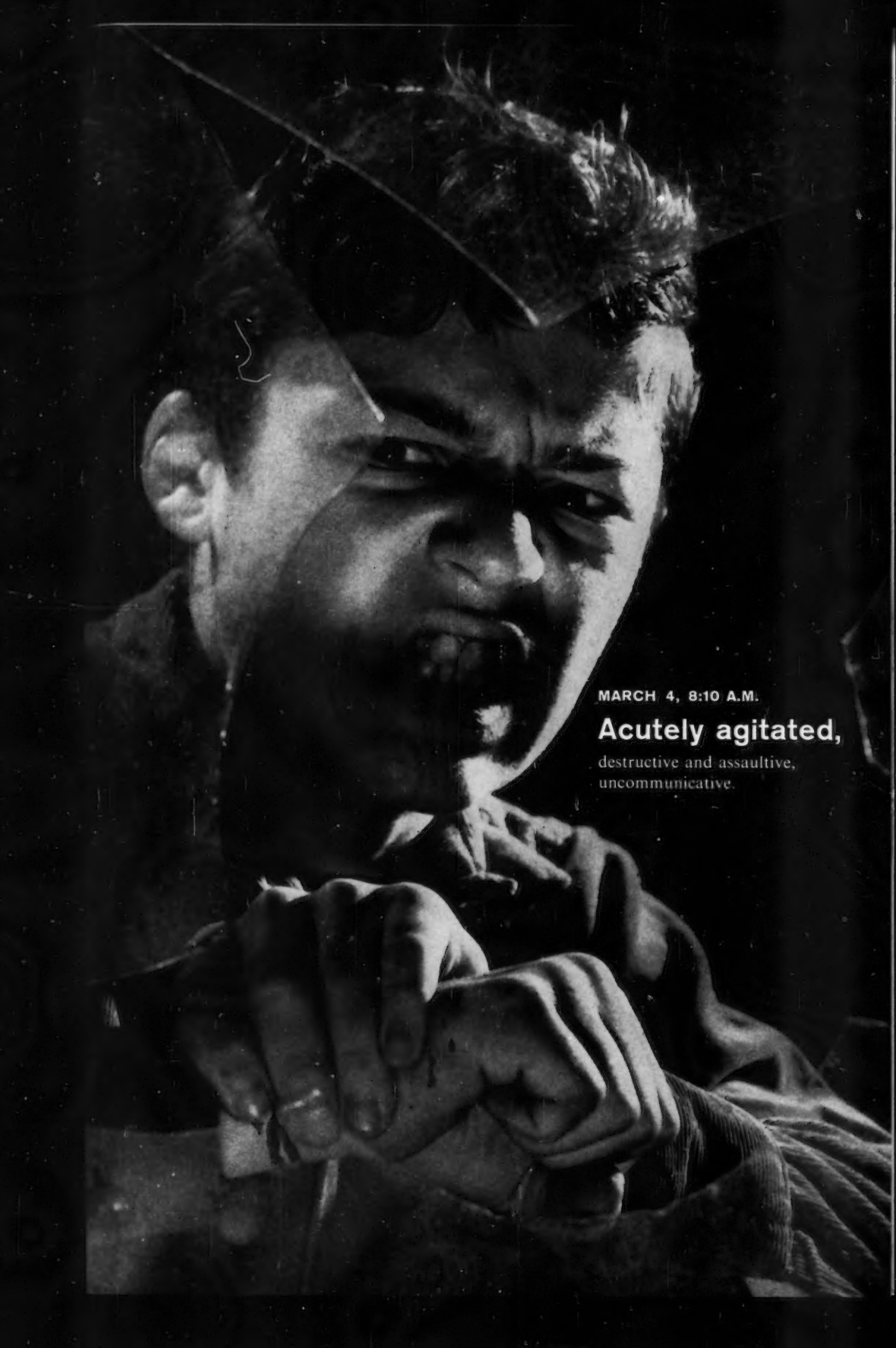
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Acutely agitated,
destructive and assaultive,
uncommunicative.

ARCH 4, 10:00 A.M.
PARINE, I.V., has been given.
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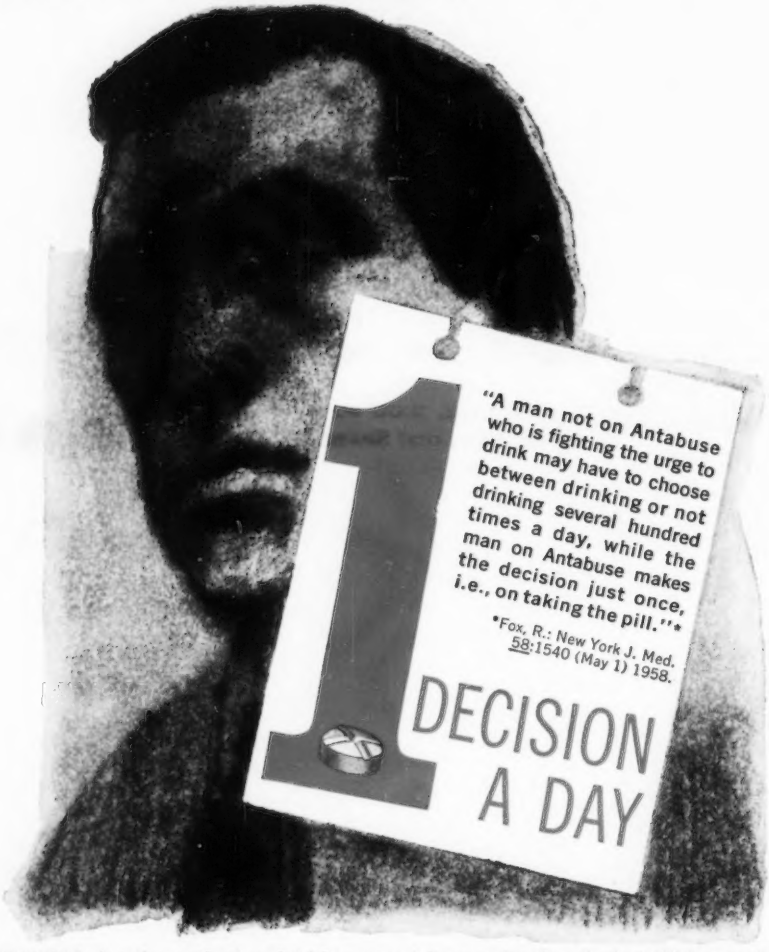
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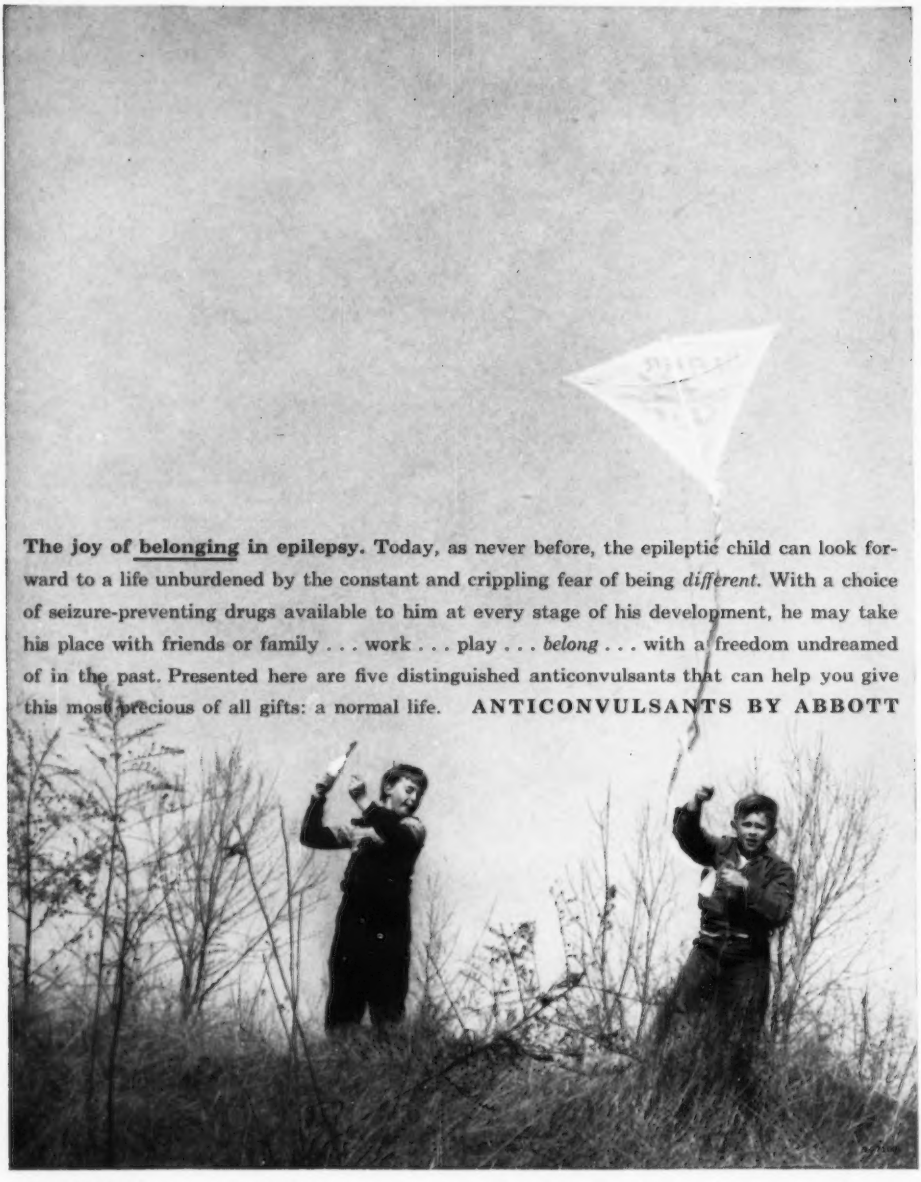

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chemistry-pharmacology: Nardil, first discovered in 1956 by Scott and Chessin,[5] is beta-phenylethylhydrazine dihydrogen sulfate, a powerful inhibitor of monoamine oxidase in the brain.[6]

clinical response: many depressed patients respond with an elevation of affect within 4 to 8 hours. Self-deprecatory feelings and even suicidal ideation rapidly subside. Depression is lifted without the overstimulation of sympathomimetic amines. Remission generally occurs within 2-6 weeks.

side effects, toxicity: clinical trials since 1957 have revealed no toxic effects on blood, liver or kidneys. Few side effects have been encountered. However, dosage levels higher than recommended may produce transient postural hypotension, constipation, impotence or delayed micturition.

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complete remission in 2 to 6 weeks

•

side effects transient and mild

Common among the experience reported by several investigators during the Nardil trials was this new drug's speed of action, high percentage of complete to good remissions, the relative lack of toxicity and the infrequency and mildness of side effects.

Many patients report a lift in mood within four to eight hours. A new sense of purpose is accompanied by a rapid dispersal of self-deprecatory feelings, ruminative thinking and suicidal ideation. Sleep and appetite are improved.[1]

Sainz[2] reported that, of his series of 122 patients, 89 per cent of the depressed affectives and 82 per cent of other endogenous depressions had complete remissions following Nardil.

Maximum improvement was always noticed not later than five weeks after the onset of therapy.[2] This investigator then concluded that Nardil "...appears to be a treatment which...compares to electrocoma therapy in scope, rapidity of action and freedom from serious side effects."[2]

This observation has also been made by Thal[1] as a result of his experience with Nardil in 180 patients with true (endogenous) depressions. "In the treatment of depression, the response to this antidepressant therapy approaches the response generally obtained from electro-shock therapy. Eighty per cent of patients were discharged from the hospital...within 60 to 90 days following commencement of treatment with Nardil." Electroconvulsive therapy was not used in any case.

Saunders and colleagues[3] found that all their patients with true (endogenous) depressions had complete relief of their symptomatology within 10 to 15 days of therapy with Nardil.

In over 1,000 patients to date: *liver dysfunction did not occur, clinical hypotension was rare.*

Nardil has a preferential distribution to the brain—not the liver. The investigations of Sainz[2] in 122 moderate to markedly depressed patients revealed that Nardil was well tolerated "...because no hepatic, hemopoietic or central nervous system parenchymatous damage (had) occurred or been foreshadowed." The experience of

Thal[1] in 180 patients, and that of Saunders[3] as well, disclosed no toxic effect after careful analysis of liver function tests and blood studies.

Postural hypotension has appeared among a few patients given Nardil in a dosage range higher than that recommended.[2] But since the incidence does not appear to be clinically significant, it does not detract from Nardil's particular value in ambulatory as well as hospitalized patients.

Indications: Nardil is indicated in the treatment of true (endogenous) depressions of an affectual or organic nature. Depression associated with catatonic schizophrenia may be relieved, although Nardil itself has no effect on schizophrenic mechanisms.

Side Effects: The occasional side effects which have been reported include postural hypotension with the expected associated signs, transient impotence, nausea, ankle edema, delayed micturition and constipation. These can be adequately managed by appropriate adjunctive therapy or will abate as dosage is reduced to the maintenance level.

Caution: Even though no toxic effects on the liver have been reported with the use of Nardil, as a matter of caution patients should be carefully followed with liver profile studies and the drug should be withheld or used with extreme care where the patient has a history of liver disease or where liver damage is present. Also, hypotensive patients should be under close medical supervision.

Dosage: Recommended starting dose is one 15 mg. tablet three times a day with meals. Improvement is usually seen within one week. After maximum benefit is achieved, usually over a period of several weeks, the dosage is slowly reduced to a maintenance level depending upon individual needs and may be as low as 15 mg. daily. In the occasional patient who does not respond to the above starting dose, an additional one or two 15 mg. tablets may be given at bedtime.

Supply: Bottles of 100 orange-coated tablets, each containing 15 mg. phenylethylhydrazine present as the dihydrogen sulfate.

References: 1. Thal, N.: Cumulative Index of Antidepressant Medications. Dis. Nerv. System *20*:197 (May) 1959. 2. Sainz, A.: The Phrenopraxic Activity of a Non-noxious Antidepressant, Ann. New York Acad. Sc. (in press) 1959. 3. Saunders, J. C.; Roukema, R. W.; Kline, N. S., and Bailey, S. d'A.: Clinical Results with Phenelzine, Am. J. Psychiat. (in press) 1959. 4. Report of Clinical Trials with Nardil in 800 Patients. Warner-Chilcott Department of Clinical Investigation, 1959. 5. Chessin, M.; Dubnick, B.; Dramer, E. R., and Scott, C. C.: Modifications of Pharmacology of Reserpine and Serotonin by Iproniazid, Fed. Proc. *15*:409, 1956. 6. Chessin, M.; Dubnick, B.; Leeson, G., and Scott, C. C.: Biochemical and Pharmacological Studies of β-phenylethylhydrazine and Selected Related Compounds, Ann. New York Acad. Sc. (in press) 1959.

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A.M.A. ARCHIVES OF
NEUROLOGY

Studies in Alcoholism

Effect of Amino Acids on the Rate of Disappearance of Alcohol from the Blood

JOSEPH SCHILLER, M.D., Ph.D.; ROBERT E. PECK, M.D., and MOE A. GOLDBERG, M.D., New York

The effects of various foodstuffs on the rate of alcohol disappearance from blood has been investigated in animal and in man. The utilization of glucose to which insulin is added has developed into a therapeutic technique used in the treatment of acute alcoholism.[1] By contrast, lipids have been tested to a much less extent, and the available evidence indicates that their effect on the rate of alcohol utilization is negligible.[2,3,9] Amino acids administered to experimental animals have seldom been given by infusion,[4] mainly orally,[5,6,8,9] and rarely as pure amino acids.[11] In man the oral route is the more popular one,[6,7] except postoperatively, when amino acids are administered intravenously, together with alcohol and glucose to make up the desired number of calories.[12] The oral administration of both alcohol and food has the disadvantage of obscuring the mechanism of action of amino acids on alcohol metabolism, i. e., mechanical, resulting in a retention of the ingested alcohol by the food present in the digestive tract, and chemical, resulting in the direct action of the amino acids on the rate of alcohol utilization. In the investigation reported here, the separation of these two factors was obtained by administering alcohol orally and amino acids intravenously.

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Veterans Administration Hospital, Department of Psychiatry and Neurology.

Materials and Methods

Ten men with chronic alcoholism hospitalized on closed wards, free of psychosis or physical defects, were selected for this study. Each patient had a battery of liver tests performed, and no subject deviating from the normal standards was considered suitable. No patient was admitted unless he had spent several weeks in the hospital, so as to eliminate any possible alimentary deficiency. Breakfast was not allowed on the morning of the study. Each subject was also kept in bed. Lunch was permitted three and one-half to four hours after the beginning of the study, since it was considered that all alcohol had been absorbed by that time.[13,14] The profile of the curve obtained confirms this finding.

A standard dose of 120 ml. of whisky N. F. (100 proof) was ingested within 20 minutes with 1 or 2 oz. (30 or 60 cc.) of water. In the rare instances in which vomiting occurred the study was discontinued. The amino acids (protein hydrolysates) were used as a 5% solution* and

* Two preparations were used: 1. Amigin, with a content (powder) in amino acids approximating the following distribution: leucine 9.1%, valine 5.3%, lysine 5.1%, isoleucine 4.9%, phenylalanine 3.9%, arginine 3.2%, threonine 2.9%, methionine 2.6%, histidine 1.9%, tryptophan 1.3%, glutamic acid 17.1%, proline 6.2%, serine 4.9%, aspartic acid 4.7%, alanine 4.2%, hydroxyproline 1.5%, aminoacetic acid (glycine) 0.4%, cystine 0.3%, and tyrosine 2.0%. 2. Aminosol, containing arginine 6.6%, histidine 2.9%, lysine 8.4%, tryptophan 1.2%, phenylalanine 3.3%, tyrosine 2.9%, cystine 2.7%, methionine 3.0%, threonine 5.9%, leucine 13.7%, isoleucine 5.7%, valine 5.8%, aspartic acid 2.8%, glutamic acid 5.4%, and significant amounts of aminoacetic acid, alanine, serine, and proline.

were given intravenously by the drip method over a 75- to 90-minute period in quantities of 1,000 ml. Since the amino-acid mixture is a solution in 5% dextrose, each patient received in a prior study an infusion of 1,000 ml. of 5% dextrose over a similar period of time, together with 120 ml. of whisky taken orally. Thus, each patient served as his own control. In two instances, blood sugar levels were determined at zero, one, two, and three hours and found to be, respectively, 80, 144, 175, and 105 mg. % and 93, 163, 210, and 154 mg. %. The concomitant alcohol-utilization curves did not differ from those in which whisky was given alone. Venous blood was obtained at zero, one, two, three, and five hours in dried heparinized tubes, which were immediately stoppered and stored at —5 C until processed, usually within one hour. Urine was pooled over the five-hour period and likewise kept under refrigeration. Alcohol determinations were made by an adaptation of Harger's microdichromate method.[16]

Results

In Figure 1 are shown the comparative curves of alcohol utilization respectively after 5% dextrose and 5% amino acids in 5% dextrose. It is apparent that, with one exception (Graph 9), there is more rapid utilization of alcohol under the effect of the amino-acid mixture. The characteristic features are a lower peak (Graph 9 included) and a more rapid junction with the base line (Graph 9 excluded). Another characteristic feature of amino-acid-infusion experiments is provided by the rate of renal elimination of alcohol: Independently of the total five-hour output, the per cent excretion is lower than in control experiments.

Figure 2 represents studies in which, in addition to the above-described curves (*A* and *B*), a third type of alcohol-utilization curve is represented (*C*), in which the amino-acid infusion was started one hour after the ingestion of alcohol. Curve *C* falls between *A* and *B*.

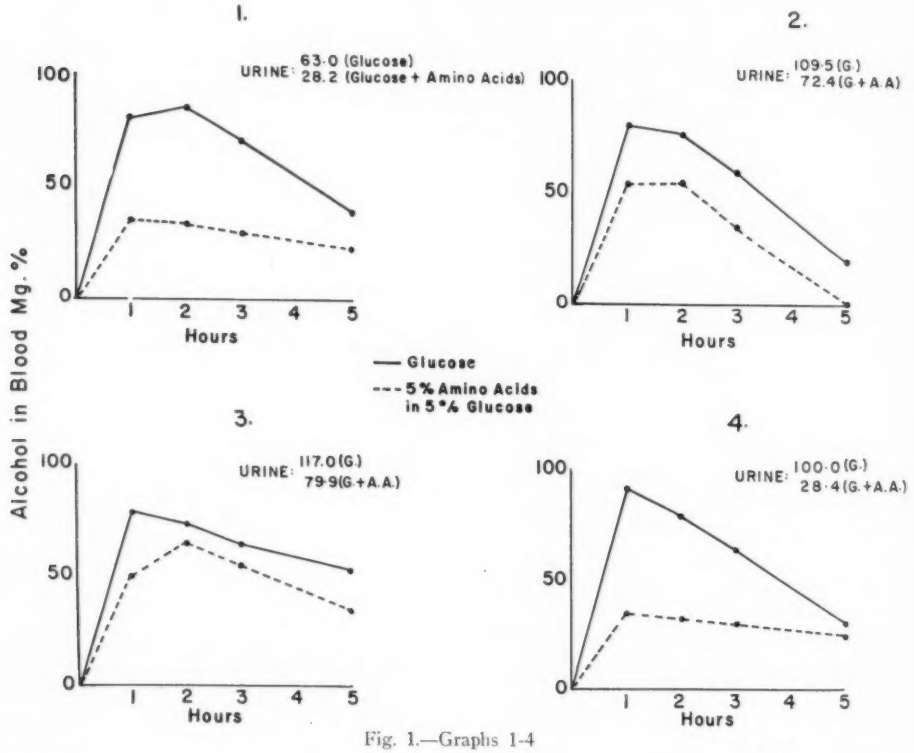

Fig. 1.—Graphs 1-4

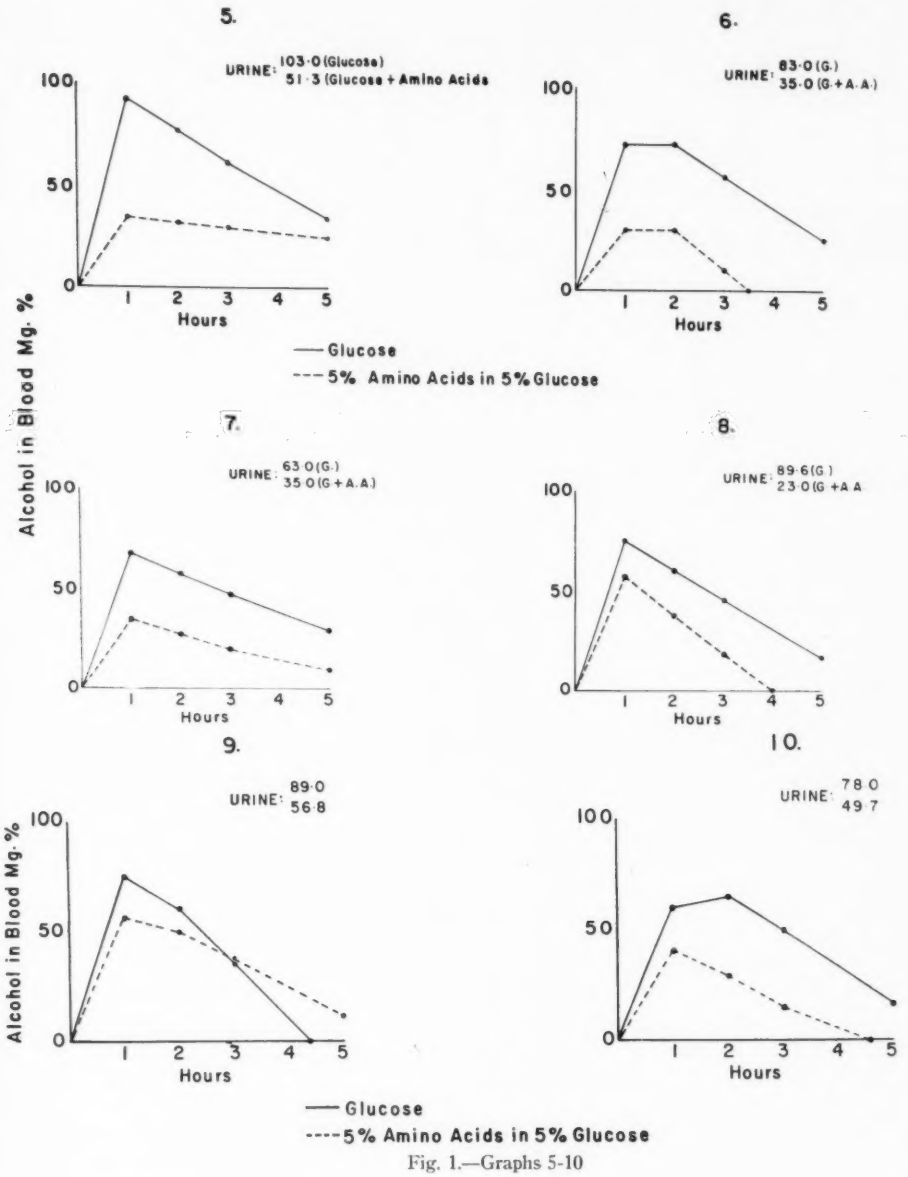

Fig. 1.—Graphs 5-10

Comment

Evidence for a possible effect of amino acids on the rate of alcohol disappearance from blood is provided by fasting and feeding studies. Dontcheff [5] has shown that in the fasted rat the oxidation of alcohol is increased by carbohydrates and proteins, not by fats, and that the oxidation of ethyl alcohol increases when the animal oxidizes its own tissue proteins. This is consistent

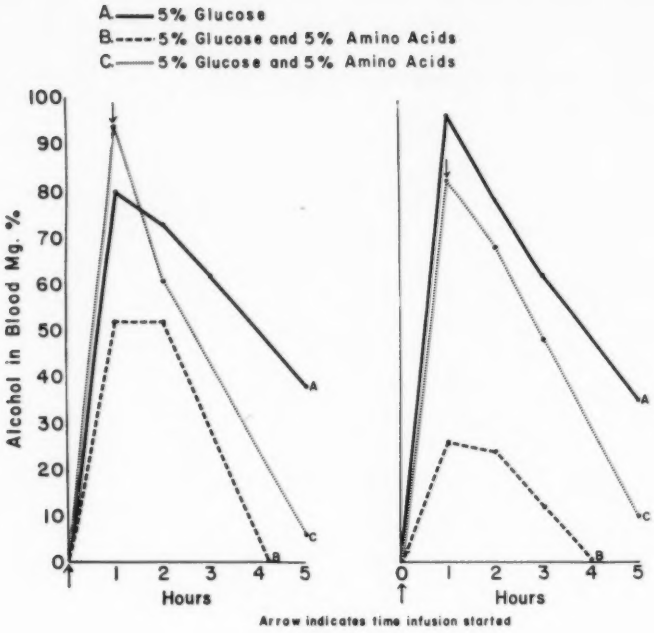

Figure 2

with the findings of Le Breton [8] and of Leloir and Munoz.[18] The interference of any absorption delay of alcohol being eliminated in our studies, the problem is that of the interaction of the amino acids and alcohol in the tissues.

The active amino acids in the mixture used cannot be identified on the basis of our studies. The role of DL-alanine has been stressed by Widmark.[9] Westerfeld et al.[10] found that DL-alanine increases the rate of disappearance of alcohol in the dog. Since the effect of DL-alanine follows a pattern similar to that obtained by the administration of pyruvate, it was concluded that DL-alanine is converted into pyruvate by oxidative deamination and that it is the availability of the latter which is the determining factor in the rate of alcohol utilization. Although Hulpieu et al.[16] and Vitale et al.[17] disagree as to the role played by pyruvate, it finds support in the work of Eggleton,[4] who demonstrated that alanine injected into cats increases the rate of alcohol disappearance, and also in the work of Greenberg [19] on the intact organism, and of Leloir and Munoz,[18] who demonstrated by in vitro experiments that both pyruvic acid and alanine increase the aerobic disappearance of alcohol when incubated with liver slices. The content of alanine used in our studies represents a quantity slightly over 4% of the total amino acids. The possibility that amino acids other than alanine are active cannot be excluded. The activity of the amino-acid mixture used in our studies was confirmed by incubating it with rat-liver slices and ethyl alcohol.[20] This was deemed necessary because Leloir and Munoz have demonstrated that, in addition to alanine and pyruvic acid, succinic, fumaric, malic, and oxalacetic acid (C-4 dicarboxylic acids) act as hydrogen acceptors and accelerate the aerobic disappearance of ethyl alcohol. In order to assay those amino acids which interchange with the Drebs cycle components, we tested the effect of glutamic acid which by deamination gives α-ketoglutaric acid. Figure 3 shows that neither with 12.0 nor with 36.0 gm.

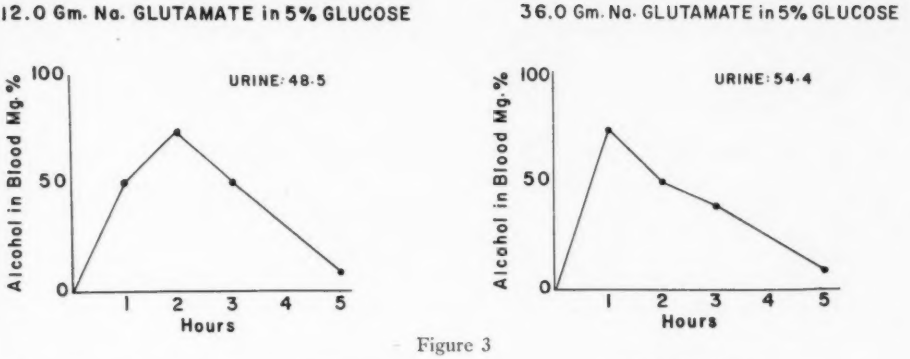

Figure 3

Na glutamate doses in 5% dextrose was there any effect on alcohol disappearance. The possibility that aspartic acid, which by deamination gives oxalacetic acid, increases the oxidation of ethyl alcohol is presently under investigation.

Summary

Ten adult chronic alcoholic men were given 120 ml. of whisky orally. Following this, 1,000 ml. of 5% dextrose solution and 1,000 ml. of 5% amino acids in 5% dextrose solution were administered intravenously on separate occasions. It was found that the amino-acid mixture decreased the concentration and increased the rate of alcohol disappearance from the blood. The 5% dextrose solution had no such effect. Also, differences in the rates of renal excretion of alcohol were found with the two types of infusion.

In another group of patients, in which the amino-acid infusion was started one hour after the ingestion of alcohol, it was found that the peaks and rate of utilization of alcohol remained unaffected during the first hour. It was accelerated during the second hour, and the curve took a position intermediate between that produced by dextrose given alone and that by amino-acid infusion started after the first hour.

Amino acids accelerate the rate of alcohol disappearance from the blood.

Miss Catherine Lynch, R.N., nurse in charge of ward, prepared the patients.

Dept. of Psychiatry and Neurology, Veterans Administration Hospital (10).

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Familial Spastic Paraplegia with Amyotrophy, Oligophrenia, and Central Retinal Degeneration

KAGE KJELLIN, M.L., Stockholm

About 200 pedigrees with familial spastic paraplegia have been recorded in the literature. In many of the cases other abnormalities were observed in addition.* Cases with coexisting spastic paraplegia and ataxia have been described as hereditary ataxia of the spastic type by Bell and Carmichael in their critical study of familial spastic paraplegia.[2]

In the present article a syndrome comprising paraplegia, amyotrophy, oligophrenia, and central retinal degeneration occurring in two pairs of brothers (A and B) is described. This syndrome does not appear to have been reported earlier.

Report of Cases

CASE A1.—The patient was a 37-year-old man, the older brother of Patient A2. According to the relatives, he had always been mentally retarded, probably with no deterioration. Since the age of 30(?) he had observed increasing stiffness and weakness in his legs when walking, especially in going down stairs. The difficulty in walking had become so pronounced that he preferred to move even short distances on a motor scooter. During the last few years the patient had noted that the thenar musculature on the right side was growing thinner. He was examined at the Neurologic Clinic, Serafimerlasarettet, at the ages of 35 and 37 years. There had apparently been slight progress in neurologic signs between the investigations.

Physical examination revealed a powerfully built man, rather corpulent but was otherwise noncontributory.

Neurologic examination showed moderate atrophy of the thenar musculature, particularly on the right side. There was suggested atrophy of the hypothenar muscles bilaterally. Fasciculations were observed in the thenar musculature on the right side. There was somewhat reduced adduction power in the thumbs, especially the right thumb. The gross strength was slightly reduced in the legs, most markedly on the right side. The muscular tonus was greatly increased in the legs. He had pronounced spastic walking difficulties, with scissors gait. The muscular reflexes in the legs were lively, with bilateral patellar clonus and subclonus in the ankles. Extensor plantar response and flexor withdrawal reflexes were present bilaterally.

Intelligence tests graded on the CVB* scale showed 75±3; i. e., the general intellectual level of the patient was very low.

Electromyography of the first interossei dorsales showed normal insertion activity. No fibrillations were observed. The voluntary activity was characterized by a reduced number of potentials; only three or four were recruited at maximum contraction, but the individual potentials attained a high frequency. Most of these had great amplitude, up to 4 mv-6 mv. The picture was typical of chronic peripheral neurogenic lesion. The anterior tibialis muscles showed a similar, but less pronounced, abnormality with a comparatively low frequency of the units, probably caused by the pyramidal lesion.

Ophthalmologic examination showed the visual acuity to be 1.0 bilaterally. The media were normal. The eyegrounds revealed about 15 small spots in the central part of the fundus, mainly within the macula and in its immediate vicinity. The largest of these were of a magnitude approximately corresponding to the diameter of the largest retinal vessels. The spots consisted of atrophic foci with pigment displacement, generally in the form of a distinct pigment deposit with surrounding atrophy. The right and left fundi presented almost identical pictures. (Examination of the eyegrounds at the age of 35 had been noncontributory.) The papillae were normal. The field of vision for white and red was normal.

The results of electroretinography indicated negativity, i. e., a comparatively pronounced a-potential.

Otoneurologic examination showed slight neurogenic loss of hearing.

The electroencephalogram showed abnormal activity in the right temporal region, with occasional bilateral shifting.

From the Department of Neurology, Karolinska Institutet, Serafimerlasarettet.

*References 2, 7, 9, 11, 17, 19-22, 25-28, 31.

*CVB=Centrala Värnpliktsbyrån (the central military service board in Sweden).

Radiographs of the skull, the spine, and the lungs were largely normal. Air myelography showed nothing pathologic except an unusually thin spinal cord, especially in the thoracic part.

The cerebrospinal fluid was normal. Wassermann reactions of the blood and spinal fluid were negative. The Sabin-Feldman dye test and the complement-fixation reaction for toxoplasmosis were negative.

CASE A2.—The patient was a 33-year-old man who had always been mentally retarded; the condition apparently did not progress. Since the age of 23(?) he had had gradually increasing feelings of stiffness and weakness in the legs.

Physical examination revealed a powerfully built man, in good general condition.

Neurologic examination showed fasciculations in the thenar musculature on the left side on some occasions. There was no demonstrable atrophy. The adduction power was somewhat reduced in the left thumb. The gross strength was slightly diminished in the legs, particularly on the right side. The muscular tonus was greatly increased in the legs. He presented pronounced spastic walking difficulties, with scissors gait. The muscular reflexes in the legs were lively, with bilateral patellar clonus. Extensor plantar response and flexor withdrawal reflexes were present bilaterally.

Intelligence tests graded on the CVB scale showed 80±3; i. e., the patient's abilities lay considerably below the average level intellectually.

Electromyography of the first interossei dorsales showed signs similar to those observed in Case A1. The anterior tibialis muscles showed nothing definitely pathologic except for a comparatively low frequency of the units.

Ophthalmologic examination showed the visual acuity to be 0.7 with correction for the right eye and 0.5 with correction for the left eye. The media were normal. Examination of the eyegrounds revealed strikingly symmetric changes in both eyes of the same type as in the brother. The foci were more numerous (about 30), however, and in general were also larger. The papillae were blurred nasally but not pathologically. The field of vision for white and red was normal.

Electroretinography showed a pronounced a-potential and normal b-potential. The ERG was negative.

Otoneurologic examination revealed a moderate neurogenic hearing loss.

EEG showed slight to moderate general abnormality, particularly in the posterior part of the right hemisphere.

Radiographs of the skull, the spine, and the lungs were normal on the whole. Air myelography showed small rounded indentations from the front into the subarachnoid space at the level of the fifth to the seventh cervical vertebrae. The spinal cord was not particularly thin.

The cerebrospinal fluid was normal. Wassermann reactions of the blood and spinal fluid were negative. The Sabin-Feldman dye test and complement-fixation reaction for toxoplasmosis were negative.

CASE B1.—The patient was a 38-year-old man, the older brother of Patient B2. He was said always to have been mentally retarded, with no progress of the condition. Since the age of 23 he had had gradually increasing feelings of stiffness and weakness in the legs. He was referred to the Neurologic Clinic at 30 years of age and was found to have spastic paraparesis with slight reduction of the gross strength. No atrophies were observed. The results of intelligence tests corresponded to a mental age of 8 years. An ophthalmologic examination showed the visual acuity to be 1.0 bilaterally, and the fundi were normal. Pneumoencephalography revealed moderate central atrophy.

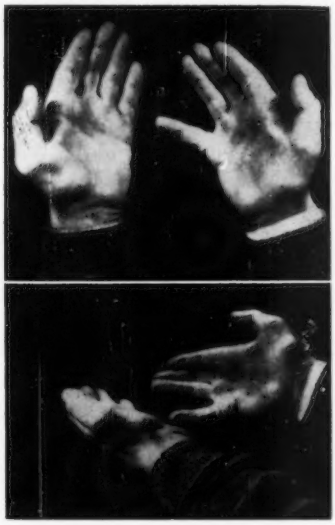
During the following eight years there was slow, steady progress of his paraparesis, and the difficulty in walking became so pronounced that he preferred to use a wheel chair. For the last two or three years the patient had noted a progressive weakness in his hands.

He was reexamined at the Neurologic Clinic at the age of 38.

Physical examination revealed a powerfully built man but was otherwise noncontributory.

Neurologic examination showed a remarkable atrophy of the small hand muscles bilaterally, particularly of the thenar musculature, and slight atrophy of the lower leg muscles (Fig. 1). Fasciculations were observed in the atrophic muscles. The gross strength was diminished in the hands,

Fig. 1. (Case B1).—Marked atrophy of the thenar musculature.



corresponding to the atrophy of the small hand muscles, and was moderately diminished in the legs. There was slight pes excavatus bilaterally. The muscle tonus was greatly increased in the legs. He could walk with the help of a stick and had pronounced spastic walking difficulties, with scissors gait. The muscular reflexes in the legs were lively, with bilateral patellar and ankle clonus. Extensor plantar response and flexor withdrawal reflexes were present bilaterally.

Intelligence tests, graded on the CVB scale, showed 69±3; i. e., oligophrenia at the borderline between mental weakness and imbecility.

Electromyographic examination of the first interossei dorsales and the anterior tibialis muscles showed signs similar to those observed in Case A1.

Biopsy specimens from the right anterior tibialis muscle did not present a picture typical of neurogenic muscular atrophy.

Ophthalmologic examination showed the visual acuity to be 0.5 for the right eye and 0.9 for the left eye. Correction glasses had no effect. The media were normal. Examination of the fundi revealed changes similar to those found in Cases A1 and A2. The right and left fundi presented almost identical pictures, with about 10 atrophic foci on each side. The papillae were normal. The field of vision for white and red was normal.

The electroretinographic examination showed a supernormal b-potential.

The otoneurologic examination was noncontributory.

EEG examination revealed a slight abnormality of bilaterally synchronous episodic type.

The cerebrospinal fluid was normal. Wassermann reactions of the blood and spinal fluid were negative. The Sabin-Feldman dye test and the complement-fixation reaction for toxoplasmosis were negative. Blood electrophoresis showed normal values except for a slight increase in the β-globulin fraction. Paper chromatographic investigation of the amino acid excretion in the urine revealed a normal amino acid pattern with relatively massive excretion of glycine.

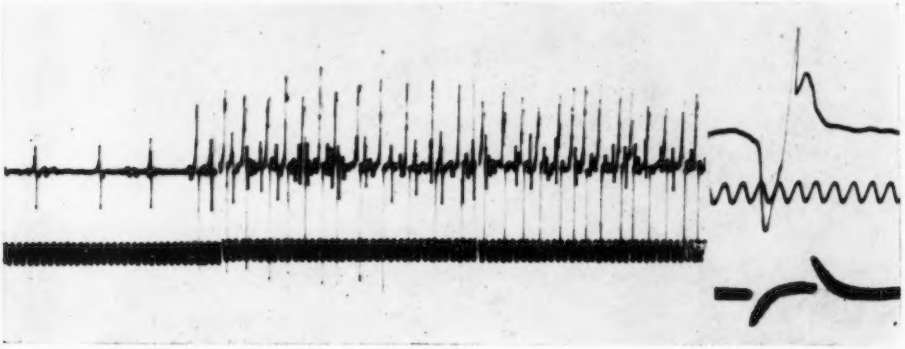
Case B2.—The patient was a 37-year-old man. According to relatives, he had always been mentally retarded, apparently with no deterioration. Since the age of 24 he had had gradually increasing feelings of stiffness and weakness in the legs. The symptoms steadily progressed, and since the age of 25 he had been unable to work. At 26 years of age he was hospitalized and was found to have spastic paraplegia with some atrophy of the leg musculature bilaterally. The results of intelligence tests graded on the Terman-Merrill scale corresponded to a mental age of 7-10 years. During recent years he had been able to walk only with difficulty with the help of two sticks. For the last two or three years he had observed slowly progressing weakness in his hands and atrophy of the small hand muscles. For some years he had also had lumbago-sciatica symptoms, with radiating pain in the right leg.

He was reexamined at the Neurologic Clinic at the age of 37.

Physical examination revealed a powerfully built man, rather corpulent, but was otherwise noncontributory.

Neurologic examination revealed a striking atrophy of the small hand muscles bilaterally, particularly of the thenar musculature, with slight clawhand flexion, especially of the two ulnar fingers on each side. Some atrophy of the thigh musculature and notable atrophy of the lower leg muscles were found bilaterally. Fasciculations were observed in arm and leg muscles. Gross strength in the hands was diminished, corresponding to the atrophy of the hand muscles. It was moderately diminished in the hip joints and strikingly diminished in the knee, foot, and toe joints. He had

Fig. 2.—Electromyographic records from the first dorsal interosseous muscle (Case B2). Voluntary activity, increasing from weak to maximum contraction. Only a few very large action potentials are recruited. Time: 1/100 second. To the right, detail picture of a large potential. Time: 1/500 second. Calibration: 500μv.



pes excavatus bilaterally. The muscular tonus was greatly increased in the legs. He could walk with the help of two sticks and presented pronounced spastic walking difficulties, with scissors gait. There was a right-sided gastrocnemius areflexia (cf. history), but otherwise the muscular reflexes in the legs were lively, with bilateral patellar clonus and left-sided ankle clonus. Extensor plantar response and flexor withdrawal reflexes were present bilaterally.

Intelligence tests graded on the CVB scale showed 70±3; i. e., oligophrenia at the borderline between mental weakness and imbecility.

Electromyographic examination of the first interossei dorsales and the anterior tibialis muscles showed signs similar to those noted in the brother (Fig. 2).

Biopsy specimens from the right anterior tibialis muscle revealed chronic neurogenic muscular atrophy.

Ophthalmologic examination showed the visual acuity to be 1.0 bilaterally. The media were normal. Examination of the fundi revealed changes in both eyes of the same type as in the brother, with five to six atrophic foci. The papillae were normal. The field of vision for white and red were normal.

Electroretinographic examination revealed no certain abnormalities. The b-potential was comparatively pronounced.

The otoneurologic examination was noncontributory.

The results of EEG examination were normal.

Radiologic examination of the spine revealed spondylarthritic changes in the lower cervical region and in the lumbar region. Air myelography showed nothing pathologic except slight disk protrusions between C-3 and C-4, C-5 and C-6, and in the lower lumbar region.

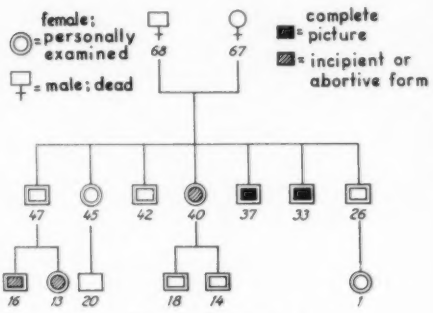


Fig. 3.—Pedigree A.

The cerebrospinal fluid was normal. Wassermann reactions of the blood and spinal fluid were negative. The Sabin-Feldman dye test was positive, with a titer of 1:10. The complement-fixation reaction for toxoplasmosis was negative. The blood electrophoretic pattern showed normal values except for a moderate decrease of α_2- and γ-globulin fractions. The electrophoretic pattern of the spinal fluid was normal. Paper chromatographic determination of the amino acid excretion in the urine revealed a normal amino acid pattern of aminoacetic acid (glycine)-taurine type. Serum copper and ceruloplasmin values were 176μg. and 0.544 (normal index 0.250), respectively. There was a normal excretion of copper in the urine (14μg/24 hr.).

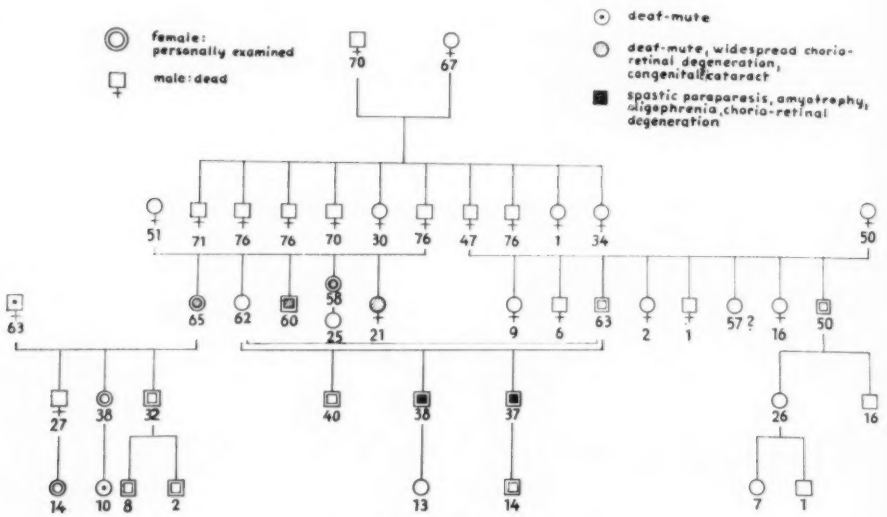


Fig. 4.—Pedigree B.

The creatine and creatinine excretions in the urine in 24 hours were 91.8 and 1,469 mg., respectively. It may be mentioned that serum creatinine, basal metabolic rate, protein-bound iodine, excretion of 17-ketosteroids and 17-ketogenic steroids in the urine, and enzyme examinations of the spinal fluid (glutamic oxalacetic transaminase [GOT], lactic dehydrogenase [LD], glutamic pyruvic transaminase [GPT], and alkaline phosphatases) were normal.

The Pedigrees

FAMILY A (Fig. 3).—There was no known consanguinity between the parents, who came from different counties. A family investigation was noncontributory except that the diseased brothers had a sister with an extensor plantar response on the right side and a niece and nephew with lively muscular reflexes in the lower extremities.

FAMILY B (Fig. 4).—The parents were first cousins. The maternal sibs all were deaf-mutes with impaired vision, which had been observed from early childhood. The visual failure had progressed during life to near amaurosis. The youngest sister died with pulmonary tuberculosis at the age of 21, but the other three sibs were still living. They all were about 60 years old and showed similar ophthalmologic signs, with bilateral cataract, mainly centrally distributed, and with widespread retinal pigmentation in both eyes. The cataracts complicated the inspection of the eyegrounds, but the pigmentation seemed to be centrally concentrated, and the periphery of the fundus was almost free from pigmentation. A physical and neurologic examination revealed nothing but very slow reaction of the pupils to light. A brother and sister were treated in a mental hospital, and the diagnosis was oligophrenia and psychosis, probably schizophrenia. The oldest sister had married a deaf-mute and had a deaf granddaughter. The mother of Brothers B1 and B2 could not be reached but was said by the relatives to be quite healthy. She had been treated in a mental hospital for mental depression some years earlier, and the general examination then was noncontributory.

Comment

The spastic paraplegia was the most conspicuous sign. It had the characteristics considered typical of familial spastic paraplegia: pronounced spasticity in the lower extremities with corresponding slight loss of gross strength (in Case B2 the decreased gross strength was apparently related largely to the amyotrophy), normal sensibility, no ataxia, normal sphincter functions, and retained abdominal reflexes. Spastic symptoms were first observed at about 25 years of age. It is probable that the onset in Case A1 could have been dated still earlier if the patient had been more observant.

Amyotrophic changes in the small hand muscles were observed as fasciculations in all four cases and in three cases (A1, B1, and B2) there was definite atrophy, particularly of the thenar musculature. Two cases (B1 and B2) also showed fasciculations and atrophy in the legs. From the electromyographic investigations it was clear that the damage to the peripheral neuron extended to both upper and lower extremities in three, and probably in all four, of the cases. Histologic examination of tissue from the anterior tibialis muscle was done in two cases (B1 and B2), revealing chronic neurogenic muscle atrophy in one case (B2) and a suspected pathologic picture in the other (B1).

Amyotrophy appears to be uncommon in familial spastic paraplegia. For example, in a series of 111 families assembled from the literature, Rhein[21] found only 9 with muscular atrophy. It is very difficult to determine, particularly in the earlier literature, whether atrophy was due only to inactivity or whether a peripheral neurogenic lesion wholly or partially caused the atrophy.

Familial spastic paraplegia with mental retardation has been reported by several writers (for instance[2,17,19,21,25,26]). In the brothers A and B this retardation was apparent from childhood, and in two cases (B1 and B2) it was observed from early childhood. There was no obvious deterioration, according to the relatives (A1, A2, B1, B2) or previous intelligence tests (B1, B2) 8 and 10 years earlier, respectively.

There was a characteristic ophthalmoscopic picture in all four cases, with central retinal degeneration, composed of small atrophic foci with pigment displacement in the macula and in its immediate vicinity. The symmetry of the right and the left fundus was remarkable in all the cases, agreeing with the heredodegenerative character of the eye disease.[29,30] Two of the patients

(A2, B1) had moderate impairment of visual acuity, but none of them had observed any visual deterioration. In two cases (A1 and B1) previous ophthalmologic examinations two and eight years earlier, respectively, was noncontributory. At the reexamination A1 still had normal visual acuity, but B1 presented moderately impaired vision. Thus, the retinal degeneration seems to have had a rather late onset and to have been slowly progressive. It should be remembered, however, that the attentiveness of the mentally retarded patients was diminished and that slight retinal changes of this type can be overlooked if the macula region is not specially examined. It should be observed that the most pronounced eye changes were found in the youngest patient (A2).

Electroretinographic examinations gave pathologic records in the patients with impaired visual acuity (A2, B1). Suspected pathologic records with similar but less pronounced changes were obtained in their brothers. The electroretinographic results indicate that the retinal changes were considerably more widespread than could be assumed from ophthalmoscopy.

There are only a few reports of retinal changes in familial spastic paraplegia in the literature, although such changes are well-known phenomena in hereditary ataxia.[4,30] The cases of retinitis pigmentosa described by Frenkel and Dide[8] and by Clauss[6] should be included among the hereditary ataxias of spastic type.[2] It is questionable whether two cases reported by Walsh[32] belong to the same group. Macular degeneration has been observed by some writers.[12-14] Peskin[18] reported disseminated choroiditis in a patient who also had tremor and generalized convulsive attacks. Autopsy revealed chronic leptomeningitis. Accordingly, this case was not one of typical familial spastic paraplegia, and the possible influence of coincident external factors cannot be eliminated. Van Bogaert[5] reported a case with *"légère choriorétinite poivre et sel des deux côtes"* (a slight pepper-and-salt chorioretinitis bilaterally).

Central retinal degeneration of the type described in my cases seems to have been observed only extremely rarely. Indeed, only two similar descriptions were found in the literature.

Schaffer[23,24] reported central choroiditis in one of two diseased brothers. In the only paper[23] in which the eye changes are described in detail, it is said that *"im linken Fundus befindet sich von der Papille temporalwärts ein etwa ¼ papillenbreiter Pigmentherd, dessen Zentrum etwas heller ist: um den Herd herum einige punktförmige Pigmentationen"* (in the left fundus temporal to the papilla is found a pigmented focus about one-fourth the diameter of the papilla, the center of which is somewhat lighter; around the focus are some punctiform pigmentations). Schaffer says that it *"dürfte sich um eine angeborene Retinalveränderung handeln"* (is probably a congenital retinal change).

Sjögren and Larsson[28] described retinal changes in 3 of 13 ophthalmologically examined cases of oligophrenia, congenital ichthyosis, and spastic disorders. In two patients[27,28] (sisters) there were changes in both fundi, but in one patient[28] (the only proband of a pedigree) only the right eye was affected, with some small aggregates of pigment and atrophy in the macula. The bilaterally affected cases showed some pale areas of atrophy of the pigmented epithelium in the macular region. The writers conclude that a pleiotropic manifestation of one main gene seems to be the mostly likely explanation of the simultaneous appearance of the main syndrome and the eye disease.

In each pair of brothers there was a remarkable symmetry with respect to the various symptoms and signs. In the A cases the spastic paraplegia, the amyotrophy, and the oligophrenia were not so marked as in the B cases, while the retinal changes were more conspicuous. There was also a striking resemblance in appearance, speech, and facial expression between diseased brothers. This "double phenomenon" has been described earlier in familal spastic paraplegia (Bickerstaff[3]).

The family investigation gave largely negative results in Family A, but the occurrence of a positive Babinski sign in a sister of the diseased brothers and lively muscular reflexes in the lower extremities in a niece and a nephew might possibly be interpreted as abortive or incipient forms of the disease. In Family B the mother's brother and sisters all had congenital deafness, widespread retinal degeneration with central(?) concentration, and mainly central (congenital?) cataracts. Two maternal sibs also were mentally retarded and psychotic (schizophrenic?). The retinal changes seemed to progress during life, corresponding to a visual deterioration. A granddaughter of a maternal aunt was deaf and dumb.

Familial spastic paraplegia with deaf relatives has been described by some writers.[1,10, 15,16] The cases reported by Appel and van Bogaert [1] also presented mental retardation. No combination of deafness, cataracts, and retinal changes seems to have been reported previously in pedigrees with familial spastic paraplegia.

It is well known that retinitis pigmentosa is often combined with deafness, and sometimes with cataract.[30] The retinal degeneration observed, however, with the central concentrated pigmentation, does not look like retinitis pigmentosa. Possibly there is an etiologic connection with the syndrome discussed. The dissimilar appearance of the retinal changes might then be explained by the difference in age, for the examined deaf-mutes all were about 60. With respect to the uniform symptomatology in the Cases A and B, on the other hand, it seems possible that there might be a coincidence of different diseases.[28]

Considering this uniformity of the symptom picture in the Brothers A and B with the lesions localized to ectodermal derivatives, it seems possible that the syndrome is caused by a simple gene anomaly. The dissimilar time of onset with respect to the separate signs could then be explained by difference in the sensibility of the damaged structures.

Summary

An apparently new clinical entity found in two pairs of brothers is described. The material is too limited to permit definite conclusions on the heredity, but it seems probable that there is a recessive heredity with an underlying simple gene anomaly. The different parts of the syndrome are as follows:

1. Nonprogressive mental retardation.
2. Spastic paraplegia, with onset of symptoms at about 25 years of age and with rather slow progress.
3. Slowly progressing amyotrophy, due to a peripheral neurogenic lesion, with atrophy of the small hand muscles and, in two cases, of the leg musculature. The hand muscle atrophy seems to become apparent at about 35 years of age.
4. Characteristic central retinal degeneration with small atrophic foci and pigment displacement in the macula and its immediate vicinity. The eye changes probably have a late onset and seem to progress rather slowly.

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I am indebted to Dr. Åke Björk for valuable ophthalmologic discussions.

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Experimental Focal Epilepsy in Animals

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Most investigators dealing with problems of the pathogenesis and pathophysiology of convulsive disorders have been concerned with discovering an animal preparation which, with reasonable fidelity, can mimic the chronic, recurrent, paroxysmal disturbance of human epilepsy. The discovery of the aluminum hydroxide technique by the Kopeloff's [1] was a fundamental advance in this regard. Local injection or application of alumina (aluminum oxide) cream will produce a chronically discharging lesion with fair regularity. However establishment of such a focus requires from six weeks to three months to develop. Once established, it may persist for at least two to three years.

Some years before this, Speranskii,[2] and more recently, in a better controlled fashion, Keith and Bickford,[3] had experimented with local cortical freezing. This method produced a local discharging lesion in a matter of hours after application but had the disadvantage of disappearing after 7 to 10 days. Both the alumina cream and the freezing techniques have the property of so altering brain tissue that the brain tissue itself becomes capable of generating a self-perpetuating epileptogenic lesion which persists after the original etiologic agent has been absorbed or has ceased to act. This is fundamentally different from the epileptiform discharges induced by electrical stimulation or by the local application of convulsant agents, such as penicillin, strychnine, pentylenetetrazol U. S. P. (Metrazol), or acetylcholine. These agents directly induce nerve-cell discharges but do not inflict long-lasting changes in neural metabolism, so that the discharges cease when the causative agent has been dispersed.

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In view of the continuing search for more workable methods of producing chronic epileptogenic alterations of nerve tissue, the following recently developed technique [4] is presented for consideration.

In a series of 66 rabbits and 15 cats discrete cortical discharging lesions have been produced by the application of an ethyl chloride spray to the pial surface. In our hands this technique has given more constant and reliable results than the simple freezing methods employed by Speranskii,[2] Keith and Bickford,[3] and others, and is simpler and easier to apply.

A small burr hole is made over an appropriate area of cortex and the dura incised and retracted. A fine spray of ethyl chloride is directed onto the pial surface until the underlying cortex whitens and swells up into the cranial opening. The spray is then discontinued, and when the cerebral swelling subsides, the dura and overlying scalp tissue are closed.

Local spike discharges may be observed beginning from one to three hours after application. Figure 1 illustrates the form of the electrographic disturbances. The drawing in the Figure indicates the placement of recording electrodes and the cortical site of ethyl chloride application. The electrodes are permanently implanted steel needles fixed in place with dental cement, and with the exposed tip resting on the dura. Recording was generally bipolar, and the channel designations are, from top to bottom: *1-3*, *3-5*, *5-6*, *6-4*, *4-2*, and *2-1*. Therefore a phase reversal between Channels 2 and 3 indicates that Electrode *5* is nearest the source of the potential disturbance, and a phase reversal between Channels 1 and 2 indicates that Electrode *3* is nearest the potential source.

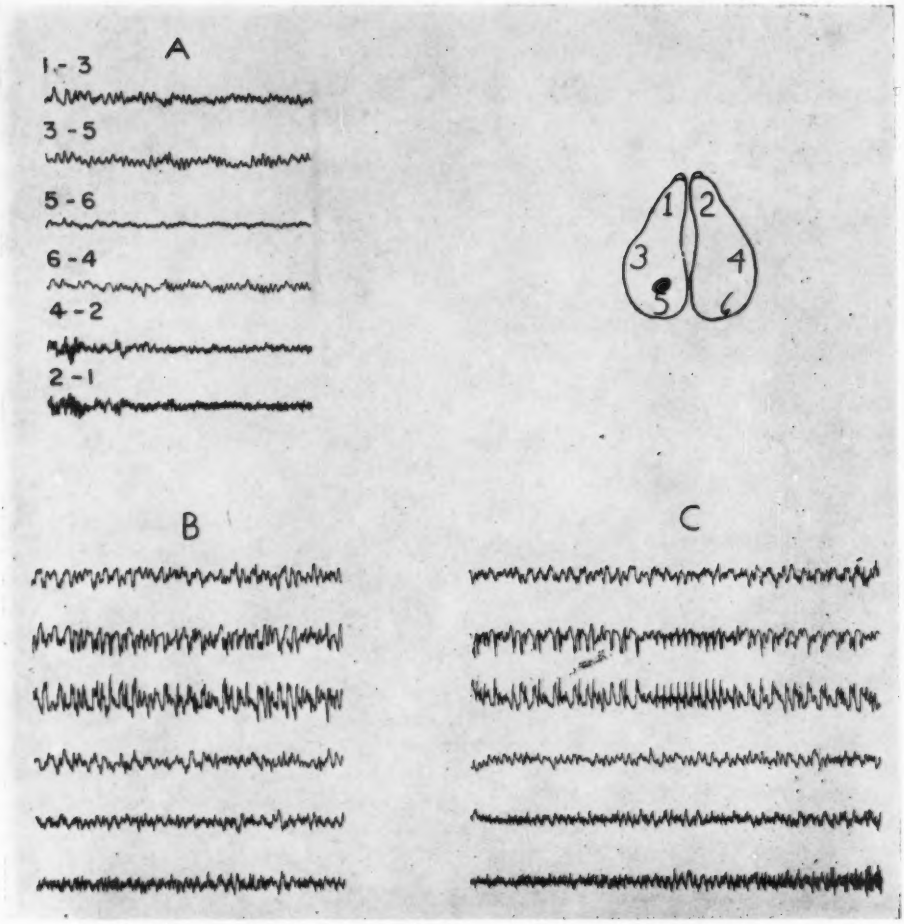


Fig. 1.—Electrographic discharge produced by application of ethyl chloride to the pial surface. *A*, control tracing before applying spray; *B*, appearance of discharge 3 hours after application; *C*, same after 12 hours.

A is the control tracing, before application of the drug. *B* indicates the electrographic discharge at 3 hours, and *C*, the discharge at 12 hours. It will be noted that a fairly constant rate of discharge persists for approximately 12-15 hours. After this time the lesion tends to vary markedly in degree of activity from moment to moment. Once the most active phase has passed, we have noted that surface leads on the scalp may record no trace of the lesion, while the implanted electrodes continue to record a localized low-voltage abnormality. However, even when apparently quiescent in the resting record, the local discharge may be discretely activated by small doses of pentylenetetrazol (5-10 mg/kg.).

The wave-form or configuration of electrical disturbance is not always that shown in Figure 1. Figure 2 demonstrates the electrographic discharge in four different animals at three hours after application. Electrode and channel designations are as before. In *A* and *C* the lesion was placed slightly more anteriorly than usual and therefore shows phase reversal at Elec-

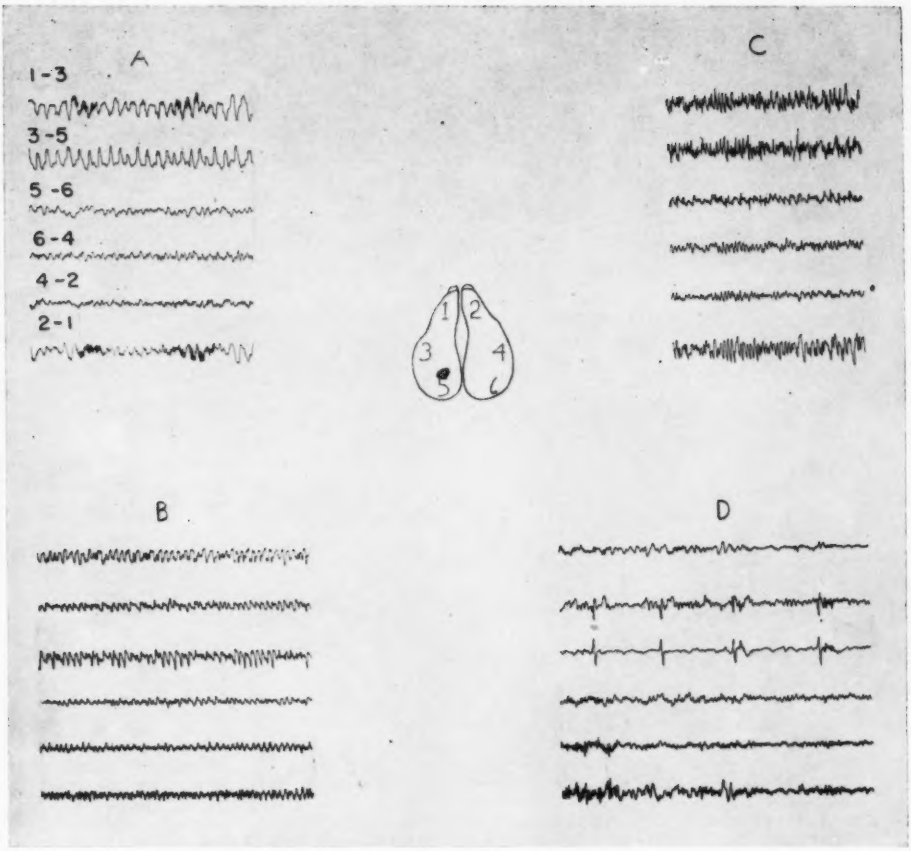


Fig. 2.—Electrographic discharge in four different animals three hours after application of spray. See text.

trode 3. *A*, *B*, and *D* illustrate different forms of electrographic abnormality in the resting record. *C* is a spontaneous focal seizure which was associated with clonic twitching of the contralateral jaw and forelimb. Spontaneous motor seizures were rare in occipitally placed lesions but common if the lesion was made closer to motor cortex.

Figure 3 is the record of an animal three months after application of ethyl chloride to the right occipital region. It illustrates the resting record and a variety of responses to photic stimulation and to Metrazol.

A is the unactivated trace (upper channel, left occipital, and lower channel, right occipital monopolar, derivations) and shows a disruption of the alpha rhythm and a mixture of slow and fast rhythms confined to the abnormal side. The left occipital tracing is normal. Photic stimulation (shown in *B*) produces a clear "driving" on the normal side but a high-voltage rapid spike discharge in the lesioned cortex. Administration of pentylenetetrazol (10 mg/kg.) produces an activation of the abnormality in the background record (Fig. 3*C* before onset of flicker) and a marked augmentation of the photic driving response in the *normal* hemisphere. (Channel designations for *C* and *D* are as follows: Channel 1—left to right occipital, bipolar;

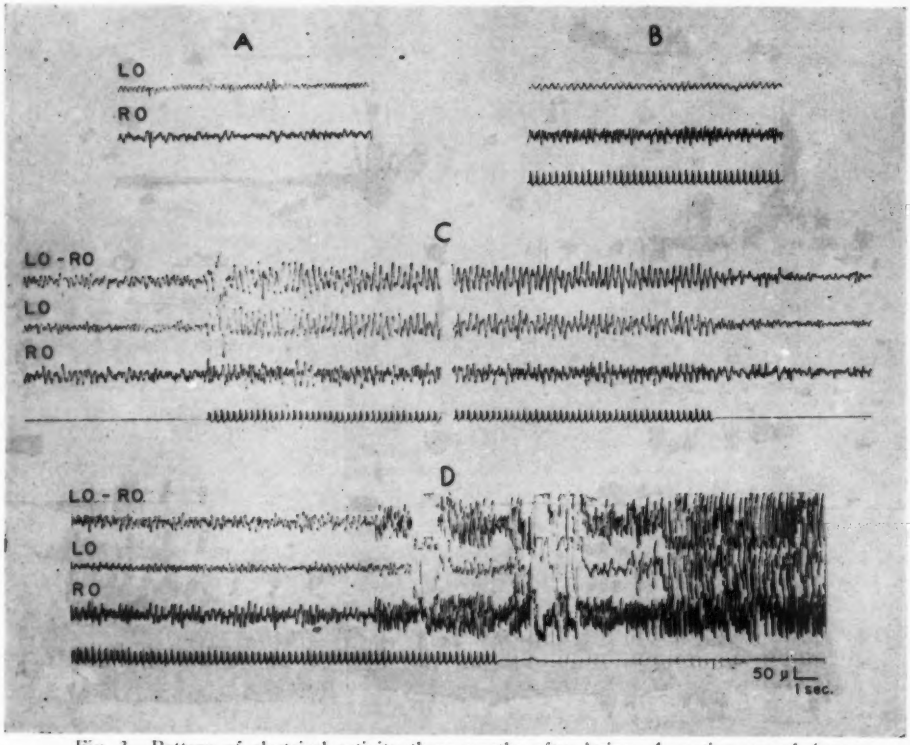
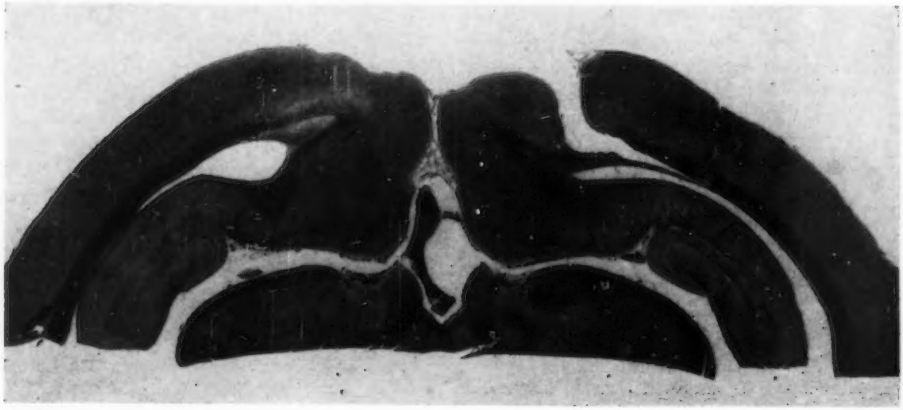


Fig. 3.—Pattern of electrical activity three months after lesion. *A*, resting record (upper channel, left occipital, and lower channel, right occipital monopolar, derivations) showing disruption of alpha rhythm on the right, or abnormal side. *B*, photic stimulation produces "driving" on normal hemisphere but rapid spike discharge in lesioned area. *C*, pentylenetetrazol U. S. P. (Metrazol) (10 mg/kg.) and photic stimulation. See text. *D*, photic stimulation eliciting a seizure, beginning locally. Channel designations for *C* and *D* are as follows: Channel 1—left to right occipital, bipolar; Channel 2—left occipital, and Channel 3—right occipital monopolar. Calibration is 50μv. and 1 second and applies to all three figures.

Fig. 4.—Myelin stain comparing area of lesion at three months with homologous contralateral cortex. See text.



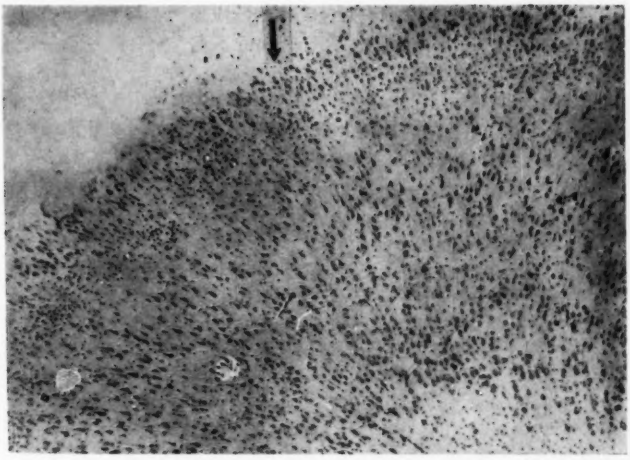


Fig. 5.—Nissl section from homologous normal cortex.

Channel 2—left occipital; Channel 3—right occipital, monopolar.) However, it is to be noted that at the end of photic stimulation an after-discharge is seen in the abnormal hemisphere, while the alpha rhythm returns promptly on the normal side. Finally (Fig. 3*D*), a prolonged photic stimulation elicits a seizure which shows a clear focal onset in the abnormal region and spreads to the contralateral cortex only after 12 seconds. Clearly, the area of the original lesion has remained selectively sensitive to the effects of excitatory stimulation, despite the fact that the resting tracing does not reveal active epileptiform discharge. This state of affairs is quite analogous to that seen in many cases of human focal epilepsy.

Histologically, the cortical lesion after three months revealed pronounced demyelination and dense gliosis, extending throughout the cortical lamina and into the subcortical white matter. A low-power Weil stain (Fig. 4) compares the normal hemisphere with the area of the lesion and illustrates the demyelination extending deep into the centrum ovale. The dura was adherent to the underlying brain, so that frequently in removal the upper cortical layers were peeled away with the dura.

Sections stained with thionine revealed a marked dropping out of nerve cells and

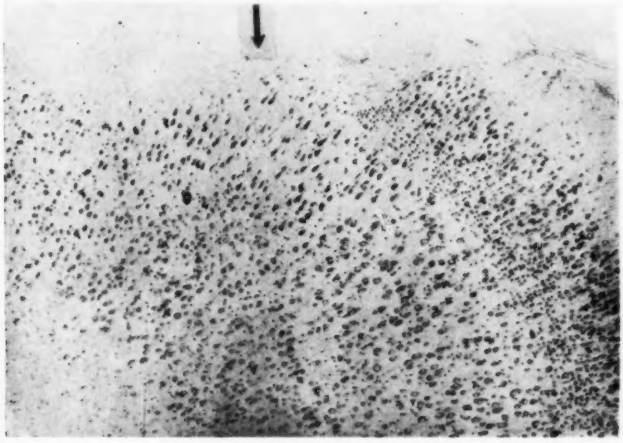


Fig. 6.—Nissl section from area of lesion.

some pyknosis and pallor in the superficial cell layers. Figure 5 is a section from the homologous normal cortex, and Figure 6, a section from the corresponding area on the side of the lesion. The degree of anatomical and histological involvement varied considerably from animal to animal, but it was often possible to restrict the lesion to 2 mm. of cortical surface and 1 mm. of depth.

Since epileptogenic lesions produced in this manner are similar both electrographically and histologically to those observed in clinical focal epilepsy, it is of some interest to speculate upon the mechanism of tissue injury so produced.

It is well known that slow freezing in cellular biological systems results in crystal nucleation primarily confined to the extracellular spaces.[5] The formation and growth of the extracellular crystal nucleus increase the extracellular osmotic pressure, so that water is withdrawn from the cell. Ordinarily the cell membrane remains intact, and the resultant high concentration of intracellular electrolyte produces a varying degree of protein denaturation and consequent disturbance of cell metabolism. The degree to which this is lethal varies considerably from species to species and with the form and rate of freezing.

Rapid freezing is defined as the rate at which ice crystals are formed intracellularly, as well as extracellularly. The rapid growth of an intracellular crystal to greater than cell size has obvious consequences for the longevity of the cell. Since the rate of freezing depends upon the initial tissue temperature and the rapidity of penetration of the freezing agent, it is likely that both slow and rapid freezing are induced in our preparation, with intracellular crystal formation more likely at superficial layers and extracellular crystal formation at deeper levels. The former would be expected to produce immediate death of cells and, consequently, the cell loss observed in our Nissl sections. At the deeper levels, however, two factors may operate to alter cell metabolism. The initially induced intracellular electrolyte concentration will result in some degree of protein denaturation, as well as an alteration of membrane characteristics, dependent upon the binding of external protein, electrolyte, and carbohydrate carried by the "obligatory" water "bound" in the extracellular crystal lattice. Since enzyme activity and cell metabolism are suppressed at low temperatures, this change is essentially a static one. However, once thawing occurs, the exposure to high electrolyte concentrations at temperature permitting enzyme activity will undoubtedly result in a far greater and a dynamic, or "phasic," type of tissue injury. Furthermore, in our preparation, the ethyl chloride itself may contribute alterations in relative electrolyte concentrations, in addition to the physical effects of freezing.

It is in the second, or "phasic," type of tissue injury, which may not always result in cell death, that we might expect to find the specific biochemical alterations giving rise to "epileptic neurons." Investigation of cell metabolism after such exposure may help to explain, for example, why protein denaturation by heat does not produce epileptogenic lesions and may lead to fundamental observations on the process of epileptogenesis in cerebral neurons.

Summary

In a series of 66 rabbits and 15 cats discrete cortical discharging lesions have been produced by the application of an ethyl chloride spray to the pial surface.

A small burr hole is made over an appropriate area of cortex and the dura incised and retracted. A fine spray of ethyl chloride is directed onto the pial surface until the underlying cortex whitens and swells up into the cranial opening. The spray is then discontinued and the dura and overlying scalp tissue closed. Local spike discharges may be observed, beginning from one to three hours after application. A fairly constant rate of discharge persists for approximately 12 hours, after which the lesions tend to vary in degree of activity

from moment to moment. However, even when quiescent in the resting record, the local discharge may be discretely activated by pentylenetetrazol (Metrazol). Evidence of localized paroxysmal activity may persist for up to three months in the cat and for at least six weeks in the rabbit. The development of a mirror focus, which persists even after ablation of the primary lesion, has been observed in the rabbit. The development of these lesions over time and responses to photic stimulation and to drug administration are described. Histological examination indicates that the lesion may be restricted to 2 mm. of cortical surface and 1 mm. of depth.

This work has been supported by The Teagle Foundation, Inc., and by the U. S. Public Health Service (Grant B1185).

University of Minnesota Medical School (14).

Addendum

Some time after this article was accepted for publication we came upon the paper of Nims, Marshall and Nielsen (Nims, Leslie F.; Marshall, Clyde, and Nielsen, Aage: Effect of Local Freezing on the Electrical Activity of the Cerebral Cortex, Yale J. Biol. Med. 13:477, 1941). These authors used an ethyl chloride spray in addition to other freezing methods and demonstrated in a small series of cats, dogs and monkeys paroxysmal discharges similar to those described in the present report.

Our laboratory (Drs. Bernard Sandler and Gilbert Ross) has recently prepared a second series of animals by applying the ethyl chloride spray to the *intact* dura for a duration of 1-2 minutes. This produces equally good electrographic lesions with somewhat less danger of infection in chronic animals.

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The Transcerebral Venous System

An Anatomical Study

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In a long-term study of the blood vessels of the brain,[1-3] contrast media were used as injection masses to demonstrate on roentgen film the course and cerebral relationship of these vessels. One of these media was a water solution of lead (lead sulfamate *), which, when injected into either the internal cerebral veins or the arteries coursing over the cerebral cortex, filled a myriad of fine venous channels traversing the white matter of the cerebral hemisphere. Interconnections between the superficial and the deep venous system of the cerebral hemispheres, through blood vessels traversing the white matter, have been postulated by others. Ekker,[4] in 1853, and Duret,[5] in 1874, presumed the presence of venous channels connecting the superficial and deep veins of the brain. Pfeifer,[6] in 1930, using microscopic methods, showed clearly anastomotic blood channels in the white matter of the brain. Schlesinger,[7] in 1939, producing venous engorgement of the veins of the brain in monkeys by ligating the internal cerebral veins, demonstrated a radiating pattern of blood vessels in the white matter of the cerebral hemispheres and regarded them as direct connections between the cortical and the deep veins. These he designated intracerebral anastomotic veins. On reviewing the available information concerning the blood vessels which traverse the white matter, it appeared that further data concerning this so-called anastomotic system would be desirable. Moreover, it seemed logical to question a direct connection between the superficial and the deep cerebral venous system inherent in the designation "anastomotic system." The present study indicates that probably these radiating channels should be termed "transcerebral veins," since anastomoses directly connecting the veins of the cerebral cortex with the Galenic system have not been conclusively demonstrated.

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From the State University of New York College of Medicine at New York City, Downstate Medical Center, and the Neurosurgical Service of Kings County Hospital.

* National Lead Company.

Materials and Method

In demonstrating the transcerebral venous system, two radiopaque substances were employed: a liquid lead compound in a vinylite-acetone solution to demonstrate the large and medium-sized veins,[8,9] and a water solution of lead sulfamate † for the fine channels within the white matter.

Fresh, untreated cadaver brains were employed. Care was taken on removing the brain not to injure the vein of Galen and its attachment to the straight sinus (sinus rectus). Under a dissecting microscope the corpus callosum was split from the splenium rostrally to about the midportion of its body, carefully protecting from damage the velum interpositum, beneath. About 2 cm. rostral to the great vein of Galen, the pial layer underlying the corpus callosum was cut and the transverse cerebral fissure entered. Two cannulae were introduced through the vein of Galen, one into each of the internal cerebral veins, and then secured by ligature. Using fresh specimens for each study, the larger vessels were demonstrated with a liquid lead

† The lead sulfamate solution consists of 174 gm. of litharge (fused lead protoxide) suspended in 150 cc. of distilled water. To this is added 75 gm. of sulfamic acid while stirring. This mixture is filtered through No. 5 filter paper and a clear filtrate obtained. The filtrate is placed in a refrigerator until it becomes cloudy (for approximately 30 minutes to 1 hour) and then allowed to stand at room temperature until two clear layers appear. The upper layer is removed, and the lower layer, containing a heavy concentration of lead, is used for injection purposes.

compound in a vinylite-acetone medium, as reported,[6] and the transcerebral venous system within the white matter, with aqueous lead sulfamate, which remains fluid in the vascular system. A small rubber connection interposed between the syringe and the indwelling cannula, for freedom of movement, is desirable. The solution was then carefully injected, using a minimum of pressure. The initial injection was watched under the microscope, thus aiding in the control of intraluminal pressure. When the large vein appeared filled, the specimen was tilted to fill the smaller vessels by gravity, although the plunger was occasionally tapped to enhance movement of the fluid. On the average, 3 cc. of medium fills the entire system. Because of the fluidity of this material, the best roentgenograms were obtained by continuing slight intravascular pressure while making the films.

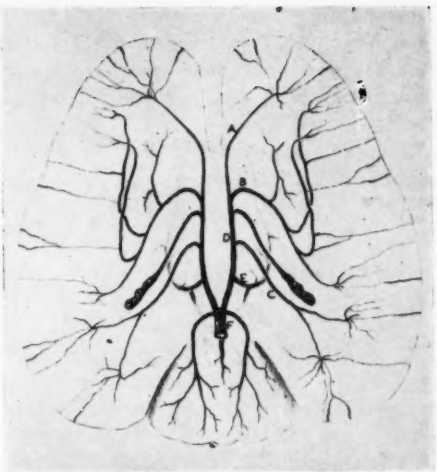


Fig. 1.—Diagram of vein-of-Galen system. *A*, anterior subependymal vein; *B*, middle subependymal vein; *C*, posterior subependymal vein; *D*, internal cerebral vein; *E*, basilar vein (vein of Rosenthal); *F*, vein of Galen.

Results

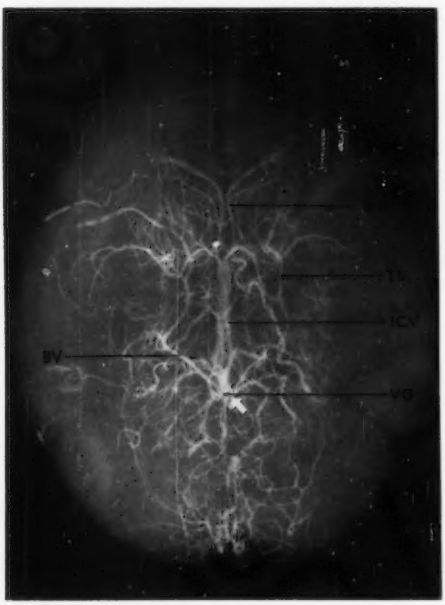
The pattern of veins traversing the white matter of the cerebral hemispheres, herein designated the transcerebral venous system, is illustrated in the accompanying diagram (Fig. 1). Extending from the entire cerebral cortex, the fine transcerebral veins tend to follow the course of the fibers of the corona radiata. These veins are demonstrated as three main groups: The first of these, the anterior group, extends from the rostral cerebral cortex through the white matter and joins with the veins from the anterior aspect of the basal ganglia to form the septal vein; the middle group of veins joins with the veins from the underlying basal ganglia to form the terminal vein; the third group of veins converge to form a vein lying subependymally just ventral to the atrium of the lateral ventricle. Some of the transcerebral veins maintain a uniform

Fig. 2.—Cross section of a hemisphere showing radiation of the transcerebral veins toward the lateral edge of the ventricle.

caliber throughout their entire length, as though in direct connection between the surface and the deep venous system; others pass from the depth of the white matter, increasing in size as they approach the cortex; still others appear to rise in the centrum ovale and become larger in caliber as they approach the collecting branches of the internal venous system (Fig. 2).

It would appear logical to label the larger collecting veins as the anterior, middle, and posterior subependymal veins (Fig. 1). The anterior and middle (septal and terminal) subependymal veins, uniting in the region of the foramen of Monro, join the choroid plexus vein to enter the rostral portion of the transverse cerebral fissure and form the internal cerebral vein. The posterior subependymal vein enters the transverse cerebral fissure more caudally to join with the internal cerebral vein (Fig. 3).

Fig. 3.—Roentgenogram of a dorsal view of the brain, showing the vein-of-Galen system following injection of a lead substance. Arrow points to site of single injection into the vein of Galen. *SV*, septal vein; *TV*, terminal vein; *ICV*, internal cerebral vein; *BV*, basal vein (vein of Rosenthal); *VG*, vein of Galen.



The veins from the cell groups at the base of the telencephalon and those from the entire diencephalon join to form the veins of Rosenthal. These latter veins, coursing around the midbrain, ultimately connect with the internal cerebral veins in the region of the dorsum of the diencephalon-midbrain junction. The internal cerebral veins then unite to form the great vein of Galen. Veins from the mid- and hindbrain do join with the vein of Galen directly or secondarily through the veins of Rosenthal.

Comment

The veins of the brain consist of two main types—the surface and the deep vessels—and are not haphazardly placed, as might be inferred from a cursory glance. While extensive collateral exists, the veins of the various segments of the neural tube grossly follow a constant pattern. The drainage of venous blood is primarily from the lateral and dorsal surfaces of the neural tube. The cerebral cortical veins have long been referred to as the surface veins, and the vein-of-Galen system, as the deep veins. Actually, the vein of Galen and the internal cerebral veins lying within the transverse cerebral fissure are surface vessels. The folding of the encephalon causes the corpus callosum to fold back over the internal cerebral veins, but they are still placed extrapially and lie on the dorsum of the diencephalon, just as the cerebral cortical veins lie on the dorsum of the telencephalon. The truly deep veins are the extensions of the internal veins lying subependymally and their tributaries from the deep and cortical cell masses. The transcerebral veins appear to be connecting channels between the cortical vascular system and the internal cerebral veins. Their function, however, is still unknown. In that the veins drain dorsomedially with reference to the neural tube and in that the cerebral cortex has migrated during its development from the deep cell masses, it is readily conceivable how these venous channels were drawn out along the course of the connecting white fibers of

Fig. 4.—Roentgenogram of dorsal view of the brain, showing the transcerebral veins joining with the veins from the basal ganglia to form the internal cerebral veins. Several white spots seen are injection artifacts. *SV*, septal vein; *BGV*, veins from basal ganglia; *TV*, terminal vein; *TCV*, transcerebral veins; *CPV*, choroid plexus vein.

the hemisphere and joined with the veins from the deep cell masses before entering the internal cerebral veins (Fig. 4). Their logical collecting site would be at the junction of the diencephalon and telencephalon (caudate nucleus-thalamus) and their entrance into the internal cerebral veins at the rostral end of the transverse cerebral fissure, again a diencephalic-telencephalic junction. The posterior subependymal vein, not often referred to by anatomists, joins the internal cerebral vein more caudally in the transverse cerebral fissure. Furthermore, the veins from the more caudal parts of the nervous system—the diencephalon, mesencephalon, and metencephalon—join with the vein of Galen in a rostrocaudal relationship, consistent with their position in the neural tube. It then becomes obvious that a pattern of veins exists in relation to the organization of the neural tube.

The transcerebral veins can best be demonstrated on roentgenograms taken of 1-in.-thick slabs of injected brains. It appeared that some of these small venous channels may be uniform in size or become larger or smaller as they approach the subependymal collecting vein. The variable appearance of these vessels may be illusions secondary to the direction of the vessel in respect to the x-ray beam. The direction of blood flow within these vessels and the terminal relationship of the transcerebral veins to the vascular system of the cortex are still unknown.

Summary

Transcerebral veins from the entire cortex of both cerebral hemispheres traversing the white matter to join with the subependymal veins of the vein-of-Galen system have been demonstrated on roentgenograms fol-

lowing injection of a radiopaque substance into the internal cerebral veins. The direction of blood flow within these vessels and their terminal relationship to the vascular system of the cortex are unknown.

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Hemorrhagic Encephalopathy Induced by Hypernatremia

II. Experimental Observations on Hyperosmolarity in Cats

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Hypernatremia as a cause of acute neurological disorder is being recognized with increasing frequency.[1-11] Common clinical and metabolic features in infants with fatal outcome were described in the previous paper.[12] At autopsy, extensive venous occlusion and subarachnoid, subdural, and intracerebral bleeding were prominent findings. Mechanisms for production of these vascular changes and their relative importance in the clinical picture were not clear. It was not known, for example, to what degree hemorrhagic encephalopathy was an integral manifestation of the underlying metabolic disturbance, or whether these vascular lesions merely represented nonspecific, secondary results of transiently disturbed intracranial-pressure relationships.

Hyperosmolarity, of order of magnitude similar to that encountered in patients (375-400 mOsm/L.), produces comparable clinical alterations in experimental animals.[13,14] Within 30 minutes after intraperitoneal injection of hypertonic solutions, cats develop marked tremor, ataxia, muscle twitching, stupor, and occasional convulsions. One cat in three dies within a few hours. In those surviving for 24 hours, the neurological abnormalities persist unabated if the solution injected contains sodium and chloride ions. When hypertonic (3 M) solution of urea is used in similar volume, however, complete clinical recovery takes place in 6-10 hours. If the vascular damage described in infants is an integral part of the destructive effects of hyperosmolarity, it should differ, at least in degree, in these two groups of animals. On the other hand, nonspecific damage to blood vessels, of considerably less clinical significance, might well follow equally electrolyte and urea injections. Such comparison is made in the present paper. Experimental hyperosmolarity of this kind in animals, moreover, allows more precise study of mechanisms involved in the vascular damage. Alterations, if any, in intravascular and cerebrospinal fluid pressure may be followed sequentially, and the pathological changes correlated with them.

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Kenny Foundation Scholar (Dr. Luttrell).

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This investigation was supported by research grants, B1409 and E1230, from the National Institutes of Health, U. S. Public Health Service.

From the Division of Neurological Medicine and the Department of Pediatrics, The Johns Hopkins University School of Medicine, and the Pediatric Division, The Baltimore City Hospitals.

Materials and Methods

Sixty-eight kittens or adult cats, weighing between 250 and 3,000 gm., were divided into the following three groups: Group I, consisting of 43 animals, received intraperitoneal injections of hypertonic electrolyte solution containing 1,500 mEq/L. of sodium, 1,000 mEq/L. of chloride, and 500 mEq/L. of bicarbonate. Group II, comprised of 16 cats, received similar injections of 3 M urea solution, the osmolar concentration being equivalent to that of the electrolyte solution. The nine animals of Group III were litter mates and were used as controls. Five were subjected to simple thirsting, and four were injected intraperitoneally with isotonic saline. All injections were adjusted by volume to 3.5 ml/100 gm. of body weight.

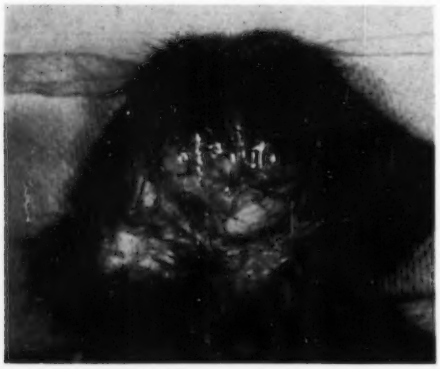
Serial changes in intravascular and spinal fluid pressures were recorded in 22 animals of Groups

I and II. Under pentobarbital anesthesia (35 mg/kg.), with the cat in a right lateral recumbent position, the cisterna magna was punctured with a No. 21-gauge needle with a collared shank and the needle connected to No. 16-gauge polyethylene tubing to form a U-tube water manometer. Patent communication was checked by respiratory and arterial blood pressure fluctuations in the height of the spinal fluid column. All pressure measurements were made with reference to zero at the level of the cisternal needle. The femoral vein and artery were cannulated with No. 16-gauge polyethylene tubing connected to water and mercury manometers, respectively. Small amounts of heparinized saline were injected periodically to prevent intravascular clotting. After control pressure measurements, nine cats were then injected with the hypertonic electrolyte solution as described above, and seven with urea. Spinal fluid, venous, and arterial pressures were recorded at five-minute intervals over a four-hour period.

In four cats receiving electrolyte injection, and in two urea injection the cisternal cannula was also connected, by a No. 21-gauge T-tube, to a 10 ml. syringe containing either liquid petrolatum (mineral oil) or isotonic saline at body temperature. Periodic introduction of fluid from this syringe prevented a fall in spinal fluid pressure throughout the experiment.

Thirty-seven additional cats from Groups I and II were used primarily for clinical studies and chemical analyses, which have been reported previously.[14] These cats, killed 24 hours after injection, and all other animals of the study, were examined at autopsy. Representative blocks of brain were immersed in 10% formol-saline, sectioned in celloidin, and stained with gallocyanin and Van Gieson's stain.

Fig. 1.—Dorsal view of the brain in situ, showing a large subdural hematoma.



Results

A. Pathology of Experimental Hyperosmolarity.—Opening the skulls of electrolyte-injected animals, the volume of grossly bloody or xanthochromic cerebrospinal fluid between the brain and the dura seemed to be increased. Such fluid accumulation was not observed in urea-injected animals. Otherwise, the gross and microscopic findings in the two groups were identical. The brain appeared retracted by some 3 to 6 mm. from the inner table of the skull. There were multiple intradural or subdural hemorrhages, measuring 1 to 10 mm. in diameter, in 48 of 53 animals. These hemorrhages were most commonly situated near the sagittal sinus, over the occipital poles and cerebellum, and at the base of the brain. Two animals injected with electrolyte solution also had massive subdural hematomas (Fig. 1). Gross intracerebral hemorrhages were present in four animals. No bleeding was seen in other body organs.

The histological changes noted in brain and membranous coverings were predominantly vascular in nature. Generalized capillary and venous stasis in the central nervous system was observed in nearly all animals from both experimental groups. Intradural, subdural, subarachnoid, and intracerebral hemorrhages were also frequently observed (Fig. 2*A*, *B*, *C*, *D*). A common abnormality was partial loss of staining reaction in the outer layer of the cerebral cortex in the depths of the sulci. This was associated with pyknosis of microglial nuclei and of occasional neurons in the outer cortical layers, and was always coexistent with intense vascular congestion of sulcal vessels (Fig. 3*A*, *B*). When subdural hemorrhages were present, this loss of staining reaction in the molecular layer was found over the surface of the gyri as well.

The control animals, five of which were subjected to simple thirsting and four injected with an equivalent volume of isotonic saline, showed none of these anatomical changes.

B. Arterial, Venous, and Spinal Fluid Pressure Changes.—Control spinal fluid pressures, measured cisternally, ranged from 10 to 90 mm. of water. The lower values in some cases resulted from inadvertent loss of a drop or two of cerebrospinal fluid when the cannula was inserted. Initial venous and arterial pressures averaged 91 mm. H_2O and 108 mm. Hg, respectively.

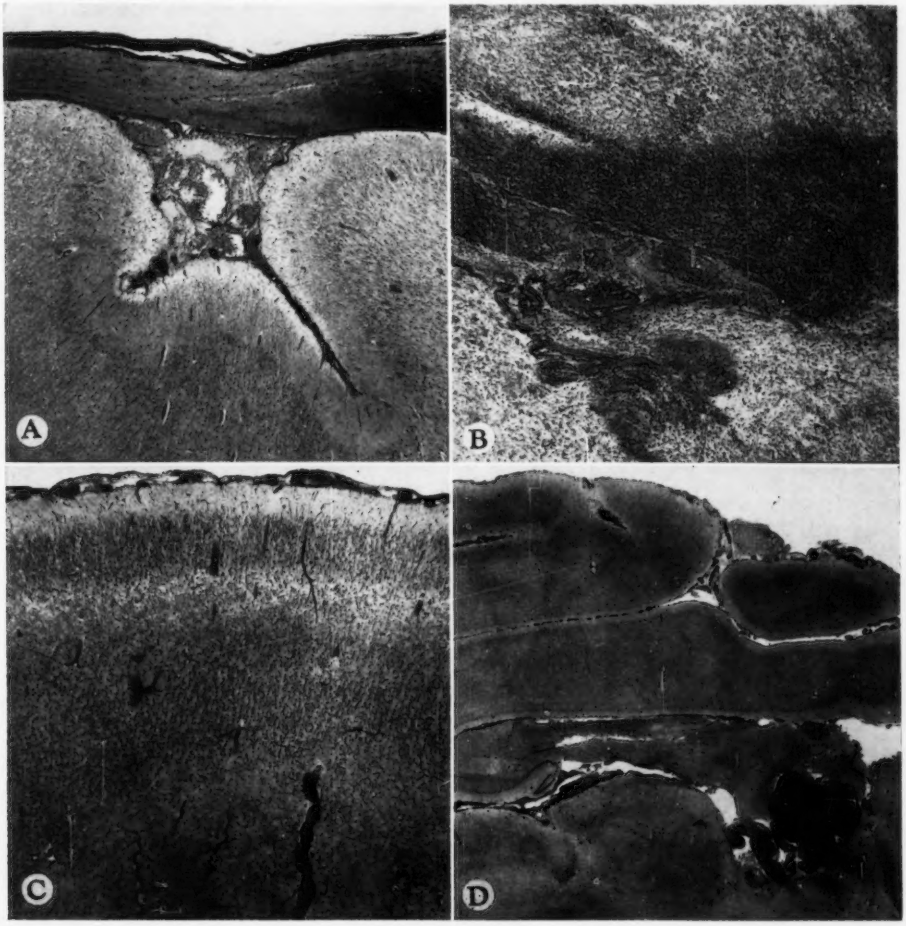
1. Changes After Hypertonic Electrolyte Injection: During the first five minutes after intraperitoneal injection, there was no consistent alteration in spinal fluid pressure. In five instances it fell slightly; in four it rose. Thereafter, within 60-80 minutes, the

Fig. 2.—*A*, section showing subdural hemorrhage, marked congestion of sulcal vessels with subarachnoid hemorrhage, and plasma diapedesis. Van Gieson stain; reduced to 79% of mag. × 35.

B, section of the dura mater, showing intradural hemorrhage. Van Gieson stain reduced to 79% of mag. × 100.

C, section through the cerebral cortex and white matter, showing intense capillary and venous congestion and subarachnoid hemorrhage. Van Gieson stain; reduced to 79% of mag. × 35.

D, longitudinal section showing intracerebral hemorrhage beneath the splenium of the corpus callosum, and generalized vascular congestion and subarachnoid hemorrhage. Van Gieson stain; reduced to 79% of mag. × 6.



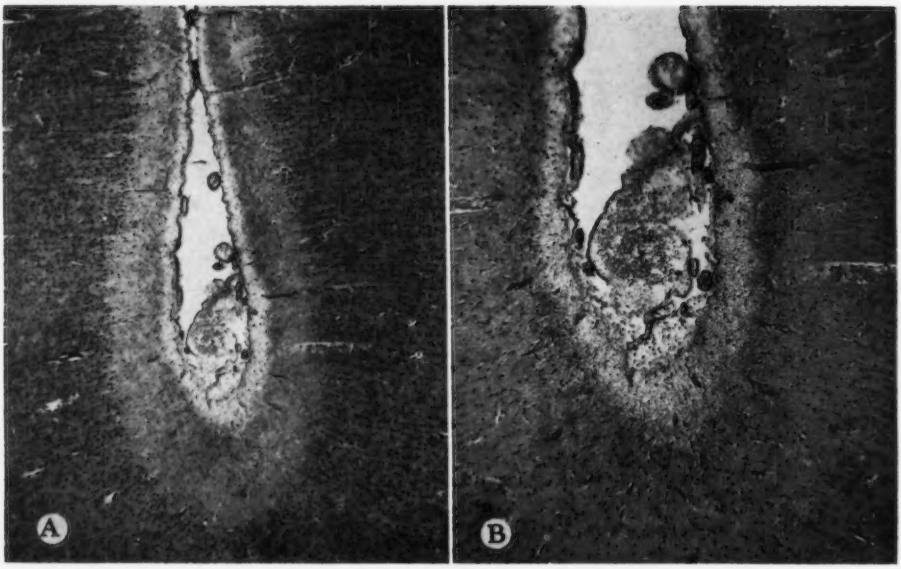


Fig. 3.—*A*, section of the cortex at the depth of a sulcus, showing congestion of sulcal vessels and loss of staining reaction in the molecular layer of the cortex. Van Gieson stain; reduced to 79% of mag. × 50.

B, higher magnification, showing loss of staining reaction in the outer layer of the cortex, and early necrobiotic changes. Van Gieson stain; reduced to 79% of mag. × 100.

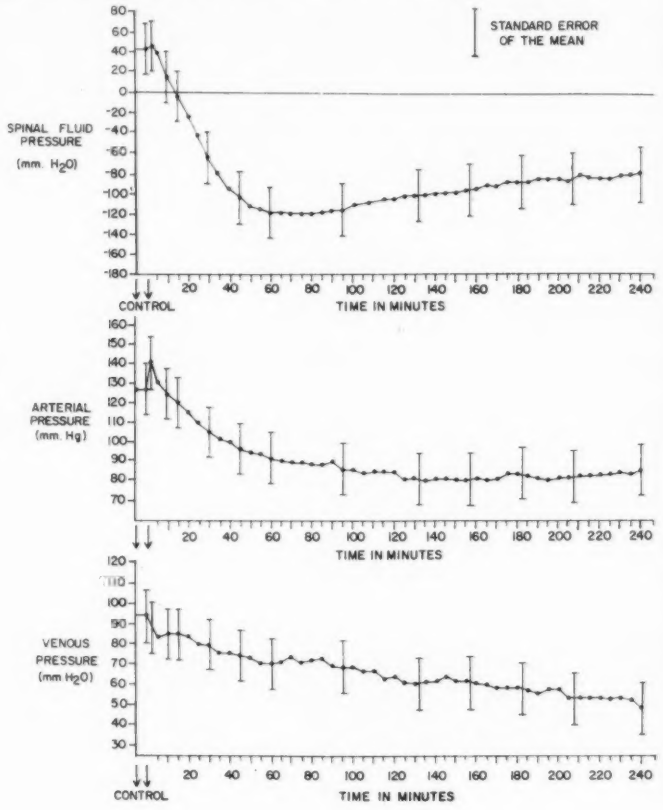


Fig. 4.—Mean alteration of spinal fluid, arterial, and venous pressures in cats following intraperitoneal injection with hypertonic electrolyte solution.

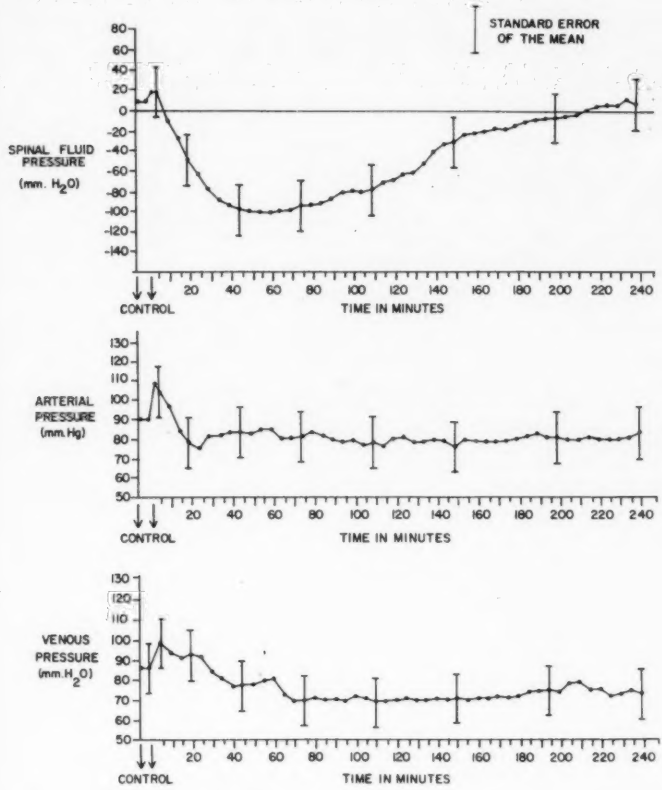


Fig. 5. — Mean alteration of spinal fluid, arterial, and venous pressures in cats following intraperitoneal injection with 3 M urea solution.

pressure fell progressively, the maximum negative pressure reaching an average of −120 mm. At the end of four hours negative pressure ranged from −20 to −155 mm. of water, with a mean reading of −80 mm. Arterial pressure, after an initial transient rise, fell steadily and remained near shock levels from the second to the fourth hour of observation. Venous pressure fell continually thoughout the four-hour period. These pressure changes are illustrated graphically in Figure 4.

2. Changes After Injection of 3 M Urea: Immediately after the intraperitoneal injection, spinal fluid pressure always rose transiently. This rise, however, was soon followed by a steady fall for about 50 minutes. Maximum negative pressure was similar in magnitude to that resulting from electrolyte injection, averaging −100 mm. of water. It was, however, of short duration. After 20-30 minutes at low levels, spinal fluid pressure began to rise once more and continued to do so for the remainder of the experiment. At the end of four hours, the pressure ranged from −40 to +38 mm. of water, with a mean value of +10 mm. There was an associated initial transient rise of arterial and venous pressure, followed by a steady fall. The magnitude of fall in intravascular pressure was comparable to that seen in the electrolyte group. The temporal sequence of these changes in spinal fluid and intravascular pressure is plotted in Figure 5.

At the termination of all experiments, regardless of whether electrolyte or urea solution was used for the intraperitoneal injection, the pathological pictures were identical. Brain retraction and intracranial hemorrhage, as already described, were con-

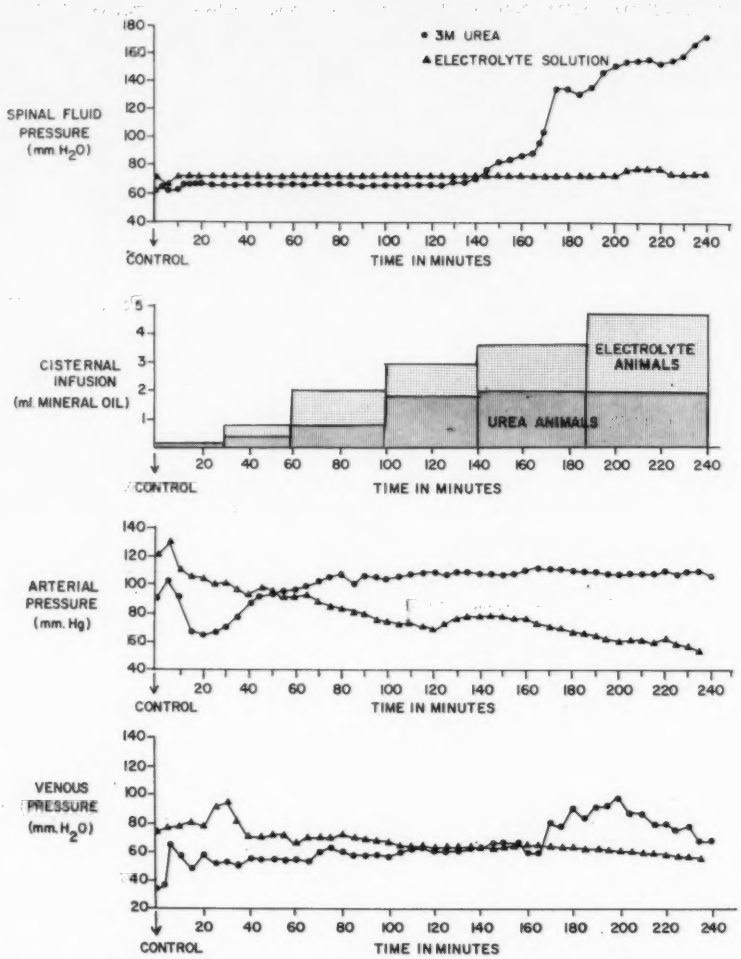


Fig. 6.—Effect of cisternal infusion with liquid petrolatum on spinal fluid and intravascular pressures, and fluid-replacement volume necessary to maintain a positive spinal fluid pressure.

sistently found, and of similar degree in the two groups.

C. Effects of Cisternal Infusion.—1. In four cats with intraperitoneal electrolyte injections, the spinal fluid pressure was maintained for four hours at a fairly constant level by frequent small cisternal infusions. Two animals received isotonic saline, and two liquid petrolatum in total quantities ranging from 4.5 to 5.0 ml. Arterial and venous blood pressure, however, fell steadily in a fashion similar to that already described.

2. Two cats with intraperitoneal urea injections also received cisternal infusions of liquid petrolatum. These animals responded differently from those which had been injected with electrolyte solution. In the electrolyte-injected animals small cisternal infusions, repeated at frequent intervals throughout the course of the experiment, were necessary for maintenance of spinal fluid pressure. On the contrary, in the urea-injected animals cisternal infusion was necessary only in the initial stages of the experiment and amounted

only to 2.0 ml. After the second hour, not only was further infusion unnecessary but thereafter the spinal fluid pressure continued to rise steadily. Arterial pressure, after an early drop, began to rise even before the rise in spinal fluid pressure. Venous pressure likewise rose, though less abruptly. These different responses in animals after intraperitoneal injections of electrolyte and urea are illustrated graphically in Figure 6.

At terminal autopsy, neither group of animals showed any evidence of intracranial bleeding. Brain weights of the six cats averaged 20 gm. There was a calculated average decrease in central nervous system water content of 23% in the electrolyte-injected cats and 10% in those receiving urea.

Comment

Brain dehydration and vascular changes accompanying hypernatremia in experimental animals have been described by others. Weed and McKibben [15,16] found shrinkage and capillary congestion after intravenous injection of hypertonic sodium chloride but no hemorrhage. They reported negative cerebrospinal fluid pressure in some animals, but the fall was considerably less than that observed in the present experiments. Girard [13] produced severe brain retraction in kittens, and also intradural and subarachnoid bleeding, by injecting hypertonic salt solution into the peritoneal cavity. He was unable to induce hemorrhage in normal kittens by simple removal of cerebrospinal fluid. He reasoned, therefore, that cerebral shrinkage within the rigid cranium, and not mere reduction in cerebrospinal fluid pressure, was the important factor in producing bleeding from dilated capillary networks. This thesis certainly receives support from the observations reported here.

Hitherto confusing, however, has been the question of the degree to which vascular damage, and consequent hemorrhage, contributes to the pathogenesis of hypernatremic encephalopathy. Both urea- and electrolyte-injected animals showed venous and capillary congestion, and intracranial hemorrhage of similar degree. The favorable clinical course of the urea-injected animals, however, differed strikingly from the adverse outcome observed in the electrolyte-injected animals. It seems evident, therefore, that the devastating brain damage of hypernatremic dehydration rests mainly on some basis other than that of visible vascular damage.[14] Nevertheless, it is apparent that this hemorrhagic encephalopathy is a common concomitant of the hyperosmolarity produced by either of the present means. It is conceivable that similar vascular damage [12] in functionally important areas may play some role in acute and chronic neurological deficits in some cases of hypernatremic dehydration.

It has been important to find in these experiments that damage to vessels and resultant hemorrhage occurred extremely rapidly after the intraperitoneal injections of hypertonic solutions. In those cats killed after four hours, the lesions were already present. It seems safe to assume, at least for the urea-injected animals, that the damage occurred during the period of precipitant drop in cerebrospinal fluid pressure —a matter of less than an hour. It is probable, therefore, that bleeding took place equally soon in the electrolyte-injected cats.

The combined effects of brain shrinkage, with stretching and tearing of fragile vessels, and distention of the vascular bed, in response to negative pressure, appear to be the cause of the intracranial bleeding. Certainly, cisternal infusion with saline, promptly begun and sufficient to maintain positive spinal fluid pressure, completely prevented the intracranial vascular damage and hemorrhagic features. It is evident that mere avoidance of negative spinal fluid pressure was sufficient to achieve this beneficial result. That it was not due to local ionic and water adjustments intracranially is shown by the fact that inert liquid petrolatum was equally effective in this regard.

In both the electrolyte- and the urea-injected animals arterial pressure fell to near-shock levels. It is true that this fall was rather more sustained with electrolyte solutions than with urea, suggesting that shock played some role in the neurological damage. Arterial blood pressure differences between the two groups were, however, relatively slight. On the other hand, cerebrospinal fluid pressure curves differed markedly. With urea injections the fall was a transient one; with electrolyte injections it persisted for at least four hours. Clearly, the difference in behavior of spinal fluid pressure, and hence volume, under similar degrees of total hyperosmolarity has something to do with differing movement of fluid into or out of cells, or subarachnoid space. In the electrolyte-injected animals there is a relative exclusion of solute from cells,[14] and hence a relative as well as absolute decrease in intracellular water. Urea, however, as a freely diffusible solute, can readily enter into brain cells. Thus, the proportionate distribution of water between intracellular and extracellular compartments is soon restored. Some of the pressure rise in the urea group can thus be accounted for basically by entry of urea into cells. Whether or not an additional factor of difference between the two solutes in the rate of equilibration between blood and cerebrospinal fluid also obtains is not known.

Summary

Kittens and adult cats with hyperosmolarity due to intraperitoneal injection of electrolyte or urea developed hemorrhagic encephalopathy.

The hemorrhages appeared to be mechanical in origin, resulting from a combination of brain shrinkage and of negative cerebrospinal fluid pressure.

Maintaining cerebrospinal fluid pressure by intracisternal infusion prevented this occurrence.

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Swelling of the Brain Following Ischemic Infarction with Arterial Occlusion

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The common concept of encephalomalacia as an atrophic or a nonexpanding lesion stems from the appearance of the lesion which has been present for a considerable time and in which a sharply delimited destructive lesion has produced decreased bulk of the brain, and perhaps even enlargement of the ventricular system toward the lesion. The appearance of the corresponding lesion of short duration has received relatively little comment, although references to its edematous appearance can be found in the old, as well as in the recent, literature.

Recent reports concerning swelling of the brain following massive infarction, often with thrombosis of the internal carotid artery, prompted the following study to determine whether such swelling was a regular occurrence following acute infarction of the brain and, if so, to determine the degree and duration of the swelling.

Method

In an attempt to limit the number of possible variable factors, only those cases were included in which there had been a sudden onset of hemiplegia, and in which at autopsy infarction was demonstrated in the classical distribution of the middle cerebral artery, including its cortical and subcortical branches. Further requirements were that the occluded vessel be demonstrated, that the infarction be purely, or almost purely, ischemic, with few or no petechial hemorrhages, and that the postmortem preservation of the brain has resulted in minimal distortion.

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Brains were dissected only after at least two weeks' fixation in 10% formalin, usually by suspension by the basilar artery. The state of the major cerebral arteries was determined after dissection. In certain cases the cervical portion of the carotid arteries was examined at the time of autopsy. Measurement of the shift of the midline was made by measuring the transverse diameter of the two cerebral hemispheres on coronal sections approximately through the center of the lesion. Corresponding points on the right and left were chosen, usually the arachnoid over the lateral fissure, and the midpoint calculated. The difference between this value and the actual site of the midline, usually the middle of the third ventricle, was then recorded as the number of millimeters of shift of the midline. The maximal amount of uncus and hippocampal gyrus medial to the groove caused by the edge of the tentorium was measured and recorded as the number of millimeters of transtentorial herniation. Similar measurement was made of the length of cerebellar tonsils beneath the groove caused by the edge of the foramen magnum.

Fifteen such cases with deaths from 18 hours to 3 months after the onset of hemiplegia have been studied to amplify the preliminary report of Shaw and Alvord,[68] and are summarized in Table 1. Two other cases are included as examples of certain problems that arise in such a study. Additional information has been obtained on 15 of the 21 cases previously reported by Berry and Alpers[6] and is summarized in Table 2.

Observations

GROUP 1: *Duration Less Than One Week.*—Eight patients died after a relatively short duration, varying from 18 hours to 4½ days (Table 3). In five of these cases death was due to embolism, in two following recent myocardial infarction, in two occurring postoperatively after mitral or aortic valvulotomy, and in one of an unidentified source. Two were due to thrombosis of the internal carotid and middle cerebral arteries associated with atherosclerosis, and another

TABLE 1.—*Summary of Autopsy and Clinical*

Case No.	Duration, Days	Shift of Midline, Mm.	Transtentorial Hernia, Mm.	Cerebellar Tonsil Hernia, Mm.	Distribution of Infarct	Type of Infarct	Vessel Occluded
1	0.7	3	10	10-16	MC	I	IC
2	0.8	7.5	11	5-10	MC	I	CC
3	1.5	7	11	14	MC	I	IC+MC
4	2	9	12	10-12	MC	I	IC
5	2	10	11	8-10	MC	I	IC+MC
6	3	7.5	0 (cing. gyr. : 6)	0	MC	I	IC
7	4.5	11	10	--	MC	I	MC
8	16	0	0	0	MC	I	MC
9	21	0	--	--	MC	I>H	MC
10	30	0	--	--	MC	I	MC
11	30	0	--	--	MC	I	MC
12	34	0	--	--	MC	H	MC
13	35	0	--	--	MC	I	MC
14	52	0	?	0	MC	I	MC
15	87	0	--	--	MC	I	MC
16	1.8	0	0	0	0	0	IC
17	26 (?)	2.5	0	0	MC	I	MC

* A, aneurysm (dissecting) of arch of aorta; E, embolus; H, hemorrhagic; I, ischemic; L, left; N, normal, 0, none; R, right; T, thrombosis; --, no data available; p. o., postoperative; CC, common carotid artery; IC, internal carotid artery; MC, middle cerebral artery.

one had occlusion of the common carotid artery at its origin by an acute dissecting aneurysm of the arch of the aorta.

In one of these cases (Case 16) no encephalomalacia was found, but in the others the area of encephalomalacia was characterized by a pale-brown discoloration and swelling of the gray matter, blurring of the demarcation between gray and white matter, and slight softening of the involved gray and white matter. In addition, there were indentation of the ipsilateral ventricle and displacement of the midline away from the lesion (Fig. 1). Frequently there was transtentorial herniation (Fig. 2).

The measured shift of the midline progressively increased with time from 3 to 11 mm. By contrast, except for Case 6, the degree of transtentorial herniation of the ipsilateral uncus and hippocampal gyrus

TABLE 2.—*Summary of Autopsy and Clinical* (Additional Data on Cases

Case No.	Duration, Days	Shift of Midline, Mm.	Transtentorial Hernia, Mm.	Cerebellar Tonsil Hernia, Mm.	Distribution of Infarct	Type of Infarct	Vessel Occluded
1	0.8	0.5	0	--	MC	I	IC+MC
2	1	6	+	--	MC	I	IC
4	1.5	0	+	--	0	0	IC+MC
5	2	3	+	--	MC	I+H	IC+MC
6	2	6	+	--	MC	I	0
7	2.2	11	+	--	MC+AC	H	IC+MC+AC
8	2.5	11	+	--	MC+AC	I	IC+MC+AC
10	3	11	+	--	MC	H	IC+MC
12	5	6.5	0	--	MC	I	IC+MC+AC
13	5.5	8	+	--	MC	I	IC
14	6	2	+	--	MC	I	IC+MC+AC
15	12	1	+	--	MC	H+I	IC
16	13	1.5	0	--	MC	I>H	CC
17	14	0	0	--	MC	H+I	IC
18	60	0	0	--	MC	I	IC

* E, embolus; H, hemorrhagic; I, ischemic; L, left; N, normal; 0, none; R, right; T, thrombosis; --, no data available; +, present, degree not stated; CC, common carotid artery; IC, internal carotid artery; AC, anterior cerebral artery; MC, middle cerebral artery; Lig., ligated; Art., arteriography.

*Data on Cases of Massive Cerebral Infarction**

Type of Occlusion	Side of Lesion	Coma	Ipsilateral Pupil	CSF Pressure, Mm.	Papilledema	Fig. No.
E	L	+ @ onset	Constricted, then dilated	--	0	3
A	L	+ @ onset	Small, then dilated	--	--	3
E	R	+ @ onset, p. o.	N	--	--	3
E	L	+ @ onset, p. o.	Both dilated	--	--	3
T	R	Somnolent	--	--	--	3
T	R	Progressive	Contralat. dilated	--	--	3
T	R	+ @ 2 days	--	510 @ 1 day	--	3
T	L	Semicoma	Both small; ptosis @ 3 days	35 @ 1 day	0	3
T	R	Confused; coma @ 1 day	Dilated @ 1 day	160 @ 2 days	--	3
T	R	Progressive	? (Eye absent)	--	--	3
T	R	Slight @ 3 days	Dilated	100 @ 3 days	--	3
T	L	Lethargic	? N (Other eye absent)	280 @ 1 day	--	3
T	L	+ @ 5 days	? (Other eye dilated and blind)	--	0	3
T	R	Somnolent, confused	Dilated	280 @ 3 days	0	3
T	R	0	N	210 @ 83 days	--	3
T	R	Confused	N	200 @ 1 day	0	4
T	R	Lethargic; coma @ 15 days	--	--	--	4

was relatively constant (10 to 12 mm.). In Case 6 only herniation of the cingulate gyrus beneath the falx cerebri was found. In three of the cases (Cases 1, 3, and 4) significant cerebellar tonsillar herniation of 12 to 16 mm. developed through the foramen magnum. In two cases (Cases 2 and 5) cerebellar tonsillar herniation was present but probably not significant.

Microscopically typical changes in neurons were seen to consist of loss of Nissl substance with general eosinophilia of the cytoplasm, a loss of the nuclear membrane, indistinctness of the nucleolus, and a general darkening of the nucleoplasm with pyknosis of the nucleus. Pericellular and perivascular spaces developed; these might represent edema fluid containing little or no protein, but interpretation of these changes in paraffin-embedded material was considered not reliable.

From the clinical point of view cases with slowly progressive or intermittent symptoms were not included in this series because of the difficulty in accurately determining the duration. Only Patient 5 had mild premonitory signs and symptoms, which were observed in the hospital to

*Data in Cases of Massive Cerebral Infarction** of Berry and Alpers[9])

Type of Occlusion	Side of Lesion	Coma	Ipsilateral Pupil	CSF Pressure, Mm.	Papilledema	Fig. No.
T	R	0	N	--	0	3
Lig.	R	--	--	--	--	3
T ?	Bilat.	0	--	--	--	4
E	R	Stupor	--	--	--	4
Art.	R	+	--	--	--	4
E	L	+	N	--	0	4
T	L	+	Dilated	140	0	4
? Lig.	L	--	--	--	--	4
E	L	+	--	140	?	3
Lig.	L	--	--	--	--	3
E	L	Stupor to coma	N	160	0	3
Lig.	R	0	--	--	--	4
T	L	+ @ onset	Contralat. dilated	175	0	4
E	R	Slight	N	145 @ onset	0	3
T ?	L	Variable; terminal coma	--	150	0	3

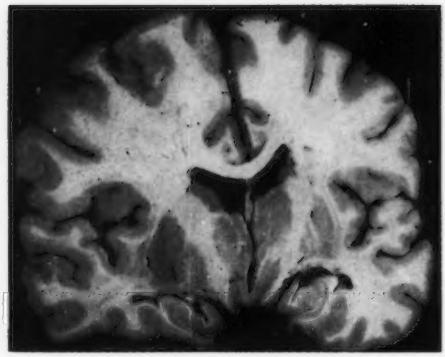

Fig. 1.—Coronal section of the brain in Case 5, showing shift of the midline away from the swollen area of massive encephalomalacia.

improve before her terminal episode. All of the patients had sudden onset of hemiplegia. Not all of the patients were examined by neurologically oriented physicians, so that comparisons are not strictly possible; but certain observations recorded in the charts are of interest with regard to evidence suggesting increased intracranial pressure, especially with transtentorial herniation (Table 3). In two of the cases ipsilateral pupillary dilation developed; in one (Case 1) of these cases the dilated pupil had first been noted to be smaller than the opposite pupil, and in the other (Case 2) both pupils had previously been noted to be small. In a third case (Case 4) both pupils became dilated, and in a fourth case (No. 6) the pupils were equal but did not react to light. The pupils were considered normal in only two cases (Cases 3 and 16) and were not described in two cases (Cases 5 and 7). In one case (Case 6) the contralateral pupil was reported to be dilated.

Changes in the pulse rate and blood pressure varied: In three cases the blood pressure rose from normal (Cases 1 and 3) or hypertensive (Case 5) levels, while the pulse rate also rose. In two of these cases (Cases 1 and 3) the pulse rate initially had been slow; and in one (Case 5) after it increased, it again became slow terminally. In four cases the blood pressure fell from hypertensive (Cases 2, 4, and 6) or normal levels (Case 7). In two (Cases 2 and 7) of these the pulse rate increased; in one (Case 4) it remained slightly rapid throughout the clinical course, and in another (Case 6) tachycardia decreased after medication. In one case (Case 16) the blood pressure fell from a hypertensive level and rose again later, the pulse rate showing no marked change. The respiratory rate and body temperature increased in five cases and remained normal in three.

In general, these patients were comatose (five patients, two not recovering from anesthesia for cardiac surgery) or deeply

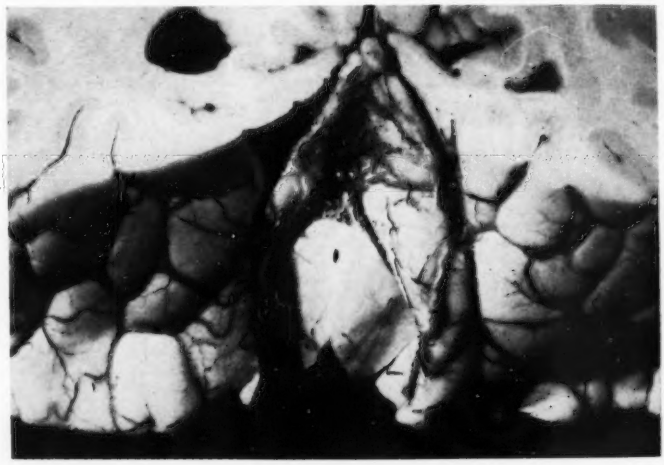

Fig. 2.—Marked transtentorial herniation in Case 5.

TABLE 3.—*Clinicopathologic Correlations in Cases of Death Shortly Following Massive Encephalomalacia*

Case No.	Duration	Herniation, Mm.			Clinical Observations						
		Shift of Midline, Mm.	Hippocampal	Cerebellar Tonsil	Ipsilateral Pupil	Blood Pressure	Pulse Rate	Resp. Rate	Temp. F°	CSF Pressure, Mm. Fluid	Coma
1	18 hr.	3	10	10-16	Constricted, then dilated	130/70→ 170/90	62→76	N	N	--	@ onset
2	20 hr.	7.5	11	5-10	Both small, then ipsilat. dilated	190/70→ 106/90	60→120	24→ 44	102	--	@ onset
3	1½ days	7	11	14	N	*140/60→ 195/90	72→180	28→ 42	98→ 105	--	@ onset (p. o.)
4	2 days	9	12	10-12	Both dilated	160/90→ 64/40	±90	32→ 44	101→ 106	--	@ onset (p. o.)
5	2 days	10	11	8-10	--	220/90→ 150/90→ 270/100	64→84 →38→60	16→28 →26	100→ 104→ 101	--	(Somnolent @ onset) †
6	3 days	7.5	0 ‡	0	(Contralat. dilated)	194/114→ 200/130→ 110/70	154→ 124→ 104	30→ 24→ 28	N	--	(Semicoma, then coma progressive)
7	4½ days	11	10	--	--	140/88→ 110/90 @ 2 days → 76/60	92→ 120 @ 2 days→ 106	26→48 @ 2 days →44	N→102 @ 2 days	510 @ 1 day	@ 2 days
16	1¾ days	0	0	0	N	210/130→ 160/90→ 220/120	N	N	N	200 @ 1 day	(Confused & disoriented)

* 70/? for 30 minutes during operation.
† Onset during sleep, difficult to arouse at 7:30 a. m.
‡ Herniation of cingulate gyrus beneath falx cerebri for 6 mm.

somnolent (two cases) from the start and became progressively worse, although in one case (Case 1) there was a transient improvement in sensorium during the first few hours. In one case (Case 16) the patient was confused and disoriented, no note being made of any change during his short course.

Lumbar punctures were made in only two patients, in both one day after onset. In one (Case 16) the pressure was 200 mm. of fluid. In the other (Case 4) the spinal fluid pressure was 510 mm. of fluid; coma developed the next day.

The cause of death in four of these patients was directly attributable to the acute infarction of the brain, and seemed particularly to be due to the swelling with increased intracranial pressure and transtentorial herniation, there being little extraneural complicating disease. Three other cases gave similar evidence of death having been due to the involvement of the brain, but they also had recent myocardial infarction (Cases 6 and 7) or aortic dissecting aneurysm with retroperitoneal hemorrhage (Case 2), conditions which also could have easily been fatal by themselves. In Case 16 there was no gross evidence of involvement of the brain, the cause of death being related to cardiac failure (chronic hypertension, auricular fibrillation, and possibly subacute bacterial endocarditis).

Eleven patients (Cases 1, 2, 4 to 8, 10, 12 to 14) reported by Berry and Alpers [6] died in less than one week. The clinical and postmortem data are summarized in Table 2.

GROUP 2: *Duration of Two Weeks or More.*—Nine cases are included, with duration of 16 days to 3 months following the onset of sudden hemiplegia (Table 4). In all of these there was thrombosis of the major arteries superimposed on advanced atherosclerosis. In one case (Case 15) the middle cerebral artery was completely occluded grossly for several millimeters, but microscopically a minute lumen within a markedly fibrotic atherosclerotic vessel was seen. In only one case (Case 17, cited below) was there evidence of increased pressure; in all the others the third ventricle was in the midline, and there was no evidence of hippocampal or cerebellar tonsillar herniation beyond that seen in neurologically normal persons studied post mortem. The cause of death was generally not directly related to the involvement of the brain; rather, death was due to complications: Pyelonephritis, uremia, and bronchopneumonia were almost constant. Clinical signs suggesting previous cerebral swelling were common, but it is difficult to know exactly how to interpret them, since they consist of relatively fragmentary observations culled from the clinical records.

TABLE 4.—*Clinicopathologic Correlations in Cases of Relatively Late Death Following Massive Encephalomalacia*

Case No.	Duration	Probable Cause of Death	Clinical Evidence of Previous Swelling
8	16 days	Pulmonary embolism, carcinoma of tail of pancreas, cachexia	? (Semicoma)
9	21 days	? (auricular fibrillation)	? (Confused, unresponsive @ onset; relatively dilated ipsilateral pupil @ 1 day; CSF pressure 160 mm. @ 2 days)
10	4 wk.	Bronchopneumonia	Semicoma @ 1 day
11	4 wk.	Nephrosclerosis, uremia, contralateral midbrain infarction 8 days before death	? (CSF pressure 11 mm. @ 3 days; relatively dilated ipsilateral pupil @ 6 days)
12	5 wk.	Uremia	? (Unconscious @ onset, lethargic @ 1 day with CSF pressure 280 mm.; right eye artificial)
13	5 wk.	Chronic pyelonephritis, atelectasis	Coma @ 5 day
14	7 wk.	Bronchopneumonia	Somnolent, dilated ipsilateral pupil @ 1 day
15	3 mo.	Pulmonary abscess, atelectasis, emaciation	0
17	(?) 15-26 days	Bronchopneumonia, uremia	? (Drowsy @ onset, transient coma @ 11 day

Case 17 illustrates some of the difficulties encountered in determining the duration of the major infarction. Three years before death the patient had a "stroke," with left hemiplegia. Thirteen days before admission he became drowsy and lethargic, and again developed a complete left hemiplegia. Two days before admission he became comatose and on admission was noted to be lethargic and to have a left hemiplegia involving the face, as well as the extremities. He died 13 days later. Multiple areas of softening were present, the oldest, in the right side of the pons, being consistent with the old left hemiplegia; a recent area of softening in the right caudate nucleus, seen microscopically, was consistent with the four weeks' duration of recurrent left hemiplegia with drowsiness, but the necrosis of the right cerebral cortex in the distribution of the middle cerebral artery seemed considerably more recent, since no gitter cells had developed, there were neutrophilic leukocytes and microglia about blood vessels, and the neurons were still visible and demonstrated ischemic changes. Although it was originally thought that the duration was 26 days, the microscopic appearance strongly suggests that the massive cortical infarction was of much shorter duration, probably less than 1 week, even though there was no dramatic clinical correlate during his two weeks of observation in the hospital.

Four patients (Cases 15 to 18) reported by Berry and Alpers[6] died after 12 days to 2 months. Their clinical and postmortem data are summarized in Table 2.

Cases of over three months' duration were not included because of difficulty with postmortem preservation of the surface of the brain, thus making it impossible to measure the degree of shift toward the atrophic lesion.

Comment

A. Pathology.—One of the major goals of this investigation has been the determination of the frequency and the temporal

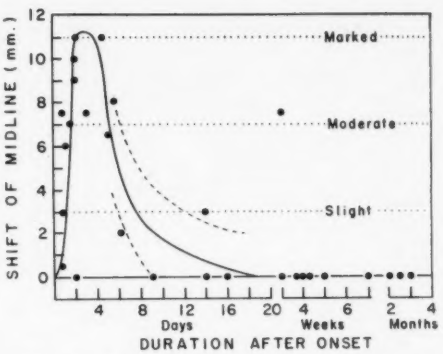

Fig. 3.—Time course of swelling of ischemic infarction in the distribution of the middle cerebral artery in cases of sudden onset with accurately known duration and with demonstrated arterial occlusion. Dashed lines indicate 2 mm. variation from the curve.

course (development and subsidence) of swelling with cerebral infarction. In order to make the series as complete as possible, the literature was reviewed and all similar cases summarized in Table 5. From the 69 cases, which include the 17 cases presently reported (Table 1) and 15 of the cases previously reported by Berry and Alpers[6] and summarized in Table 2, were selected those cases which would best demonstrate the temporal course of swelling with a relatively simple cerebral infarction.

Since it seemed likely that the amount of swelling would be directly related to the size of the infarct, and possibly also to

Fig. 4.—Time course of swelling of massive encephalomalacia in cases not completely fulfilling the criteria for inclusion in Figure 3 (see text). Dashed lines indicate 2 mm. variation from the curve.

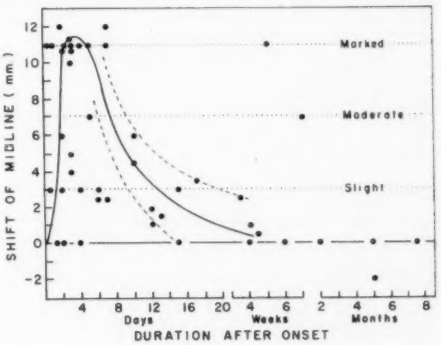

TABLE 5.—*Summary of Autopsy and Clinical Data in Cases*

Bibliographic Reference	Case No.	Duration, Days	Shift of Midline, Mm.	Basis of Measurement	Transtentorial Hernia, Mm.	Cerebellar Tonsil Hernia, Mm.	Distribution of Infarct	Type of Infarct
38 †		0.5 ?	3	Pineal	--	Prominent	MC+AC	I ?
64		0.5 ?	+	PM	--	--	MC+AC ?	I
26		0.5	Marked	PM	+	+	?	?
60	2	1	Marked	A+V	Marked	Distinct	?	I
73	4	2	12	PM	? (midbrain hemorrhage	--	MC+AC	I
32	65	2	Marked	PM	--	+	MC	I
23	8	2	0	PM	0	--	MC	I
32	42	2	+	PM	--	--	MC	I
38 †		3 ?	Marked	V+PM	--	Prominent	MC+AC	I ?
21	1	3	5	V+PM	--	--	MC+AC	I
22	3	3	Marked	PM	Marked	--	MC+AC ?	I
23	7							
19	3	3	4	V	--	--	?	?
40 †	1	3	10	A	--	--	?	?
52		4	Slight	V	--	--	?	?
63	2	4	Marked	A+PM	--	--	MC+AC	I>H
12		4	0	V	--	--	?	?
22	4	5	Moderate	PM	--	--	MC+AC	I
23	24	5	Marked	PM	Marked	--	MC+AC ?	I
32	39	5	+	PM	--	--	MC	I
19	10	6	Slight	Pineal	--	--	?	?
16 †		6	2.5	Pineal	--	--	?	?
66 †		7	2.5	Pineal	--	--	?	?
32	49	7	Marked	PM	--	--	MC	I>H
72		7	12	PM	--	--	MC+AC	I
23	5	9	0	PM	--	--	MC+AC	I
57	5	10 (?)	4.5	A (+PM)	--	--	MC	I
66 †		10	6	Pineal	--	--	?	?
19	5	12	2	Pineal	--	--	?	?
32	57	14	Slight	PM	--	--	MC	I
19	4	15	0	V	--	--	?	?
23	22	15	Slight	PM	0	--	MC+?	I
16 †		17	3.5	Pineal	--	--	?	?
73	3	21	7.5	PM	4-5	0	MC	I
32	69	28 (?)	1	PM	--	--	MC	H
40 †	1	28	0	A	--	--	?	?
16 †		32	0.5	Pineal	--	--	?	?
57	1	35	11	V	--	--	?	H ?
35	2	42	0	V	--	--	?	?
57	2	49	Moderate	V	--	--	?	I
16 †		60	0	Pineal	--	--	?	?
23	9	75	0	PM	0	--	MC	I
19	6	150	−2	Pineal	--	--	?	?
22	5	150	0	A	--	--	?	?
16 †		225	0	V	--	--	?	?

* E, embolus; H, hemorrhagic; I, ischemic; L, left; N, normal; 0, none; R, right; T, thrombosis; .., no data available; +, present, degree not stated; CC, common carotid artery; IC, internal carotid artery; AC, anterior cerebral artery; MC, middle cerebral artery; A, arteriogram; V, ventriculogram or pneumoencephalogram; PM, postmortem.

† Serial determinations in same case.

the vascular circulation within the infarct (as manifest by patency of the major arteries or by the development of hemorrhagic infarction), an attempt was made to define a standard infarct by limiting all the variables except duration and swelling. Criteria used were the presence of purely ischemic infarction in the distribution of the middle cerebral artery in cases of sudden onset with accurately known duration and with appropriate arterial occlusion. In order not to exaggerate the swelling, infarcts which might have been significantly larger than the standard one, such as those with hemorrhagic infarcts or with involvement also in the distribution of the anterior cerebral artery, were included only if no shift of the midline had occurred. Only 28 of the

*of Massive Cerebral Infarction (Review of Literature)**

Vessel Occluded	Type of Occlusion	Side of Lesion	Coma	Ipsilateral Pupil	CSF Pressure, Mm.	Papilledema	Fig. No.
MC+AC	T	R	Stupor	Dilated @ 1-2 days	82	--	4
CC+IC	E	R	Semistupor	Dilated	416	--	--
IC	T ?	--	--	--	--	--	4
IC	Trauma	R	Semiconscious	Dilated	--	Early ?	4
IC	T	L	--	--	--	--	4
IC	T	L	+ @ 2 days	Dilated	--	--	3
IC	T ?	R	Semicoma @ 1 day	--	--	--	3
IC (? bilateral)	T	R	+ @ 1 day	--	--	--	--
MC+AC	T	R	Stupor	Dilated @ 1-2 days	82	--	4
MC+AC	--	--	--	--	--	--	4
IC stenosis	T (? op. trauma)	R	+ @ 12 hr.	Dilated	--	--	4
IC	T ?	L	0	--	--	0	4
MC	T ?	R	Drowsy @ 12 hr.	--	--	--	4
MC	T ?	L	Confused	Unequal	150	--	4
MC	T ?	L	Stupor @ 3 days	--	160 @ 3 days	0	4
IC	T ?	L	0	--	--	--	4
CC+IC+MC	T	R	Confused @ 1 day, coma @ 2 days	--	N @ 1 day	--	4
IC stenosis	E	R	+	--	--	--	4
IC	T	R	+ @ 4 days	--	--	--	--
IC	T	L	0	--	--	--	4
?	T	L	0	N	160 @ 1 day	0	4
IC	T	L	0	--	N	Early	4
CC	T	R	0	--	--	--	4
CC+IC	T	R	Confused; coma @ 2 days	Dilated @ 4 days	270 @ 4 days	Slight R	4
IC	T	L	Confused	Small @ 1 day	--	--	3
0	0	L	0	Dilated	220 @ 1-2 days	0	4
IC	T	L	0	--	--	--	4
IC	T ?	L	0	N	--	0	4
MC	T	--	Restless	--	--	--	3
IC	T ?		0	N	--	0	4
CC+IC	E ?	L	--	--	--	--	4
?	T ?	L	0	N	--	0	4
IC	T	L	--	--	--	--	3
IC+MC	E	L	--	--	--	--	4
MC	T ?	R	Drowsy @ 12 hr.	--	--	--	4
?	T ?	L	0	N	--	0	4
?	?	R	0	--	200 @ 5 days	2 D.	4
IC	T ?	L	0	--	--	--	4
?	T ?	R	0	Contralateral dilated	280 @ ?	0	4
?	T ?	L	0	N	--	0	4
IC	T, E ?	R	Confused	--	--	--	3
IC	T ?	L	0	N	--	0	4
IC	T ?	L	Confused @ 1 day	--	N	--	4
?	T ?	L	0	N	--	0	4

69 cases fulfilled these criteria: 15 from Table 1, 7 from Table 2, and 6 from Table 5.

Figure 3 demonstrates the emporal course of swelling in these 28 cases of a relatively uniform ischemic encephalomalacia. It is obvious that practically all of the cases fit a curve which defines the onset and duration of shift of the midline to the side opposite the swollen area of encephalomalacia. Only one case (Case 3 of Wood [73]) stands out as an exception, the data not being adequate to account for this discrepancy.

Since the above considerations are based on only a minority of the available cases, Figure 4 was prepared from the other 48 observations in 41 cases in order to represent fairly all of the available data concerning incidence and severity of swelling. In these cases the data are incomplete (due mostly to lack of postmortem confirmation),

or the infarction contained petechial hemorrhages or involved the distribution of the anterior cerebral artery also, or no occluded artery was demonstrated. For these reasons, it was anticipated that the cases in Figure 4 would show much more variation than those in Figure 3, but actually the similarity is remarkable, all the more so when one considers the variety of conditions under which different observers have obtained the data. Only a few cases of less than two days' duration and only five cases with durations of two to four weeks show more marked shift of the midline than is represented by the curve. One of the latter (Case 17, Table 1) was clearly demonstrated by histologic study to have had an erroneous apparent duration, since a second massive cortical infarction was superimposed on an earlier small infarct in the internal capsule. With a shorter duration for the infarction, this case would fall very closely in line with those of Figure 3. Such an explanation may account for the other cases of long duration with excessive swelling, but the data are not adequate. One can only say that in those few cases in which specific information is available neither hemorrhagic infarction nor infarction including also the distribution of the anterior cerebral artery accounts for the increased swelling.

How can one account for the reverse situation, the occurrence of much less swelling than would be expected for the duration? If one considers deviations from the curve of more than 2 mm. as significant, seven cases in Figure 4 and one case in Figure 3 had significantly less swelling than one would have expected. Many other cases in the literature might have been included if it were assumed that the lack of specific mention of swelling meant that swelling had actually been absent, but this assumption seems unwarranted. Further examination of the cases considered reveals that five of the seven cases in Figure 4 are based on only clinical evidence of ventricular or pineal displacement at four,[12,52] six,[16,19] and seven[66] days' duration, with no evidence concerning the real size of the cerebral infarct. There are, therefore, only three cases with anatomic evidence that the infarct was actually in the distribution of the entire middle cerebral artery, and not just of its subcortical capsular branches. It is of interest that all three patients died in one and a half to two days; but before one can use this fact as an indication of the absence of swelling with cerebral infarction, these cases should be considered in more detail. One (Case 8 of Fisher[23]) cannot be explained on the basis of the available data, but the second (Case 4 of Berry and Alpers[6]) can be easily explained because there was bilateral occlusion of the carotid arteries. Although this case has previously been interpreted as one of edema without infarction it would seem quite possible that infarction had produced the edema, but, being bilateral, the edema could not be manifested by shift of the midline. The third patient (Case 16, Table 1) almost undoubtedly died of myocardial infarction and not of cerebral involvement. One can only speculate, since the clinical data are sketchy, whether this was an example of only transient paralysis of function, the actual duration of cerebral ischemia having been too short for irreversible encephalomalacia to occur. In summary, then, there is very little evidence that swelling does not occur rather regularly with massive encephalomalacia.

Of interest, also, is the development of transtentorial herniation. It was recorded in 20 cases (Tables 1, 2, and 5) and was specifically recorded as not being present in only 7 cases in which death occurred during the first two weeks. Not only does transtentorial herniation occur, but it seems to develop more rapidly than does shift of the midline, as judged by an almost constant amount of herniation (10 to 12 mm.), regardless of the duration of life. Apparently it is easier for the hippocampal formation to displace fluid from the cisterna ambiens, probably through increased rate of absorption, than it is for the midline to shift into the relatively noncompressible cerebral hemisphere.

Cerebellar tonsillar herniation was less regularly recorded. It was noted in 10 patients dying during the first three days and was specifically recorded as not present in only two patients dying during the first two weeks.

Review of Literature: Review of the literature makes it obvious that the reported observations are not new; and, indeed, the concept that duration significantly alters the appearance of a lesion is far from novel. Even the simple measurement of the degree of swelling and the correlation of this with the time of onset is not new: Such correlation has been done in a small series of monkeys (Harvey and Rasmussen [27]), but only one study in man (Elvidge and Werner [19]) has been encountered in which this objective was attempted. Because of possibly marked variation in the size of the encephalomalacia following occlusion of the internal carotid artery, it has been difficult to evaluate the variations reported in this radiographic study in which postmortem confirmation was not possible.

Although it is generally agreed that swelling is characteristic of recent encephalomalacia, there is little agreement concerning its severity, duration, or possible clinical correlates. Unfortunately, the descriptions given by many authors give little indication as to its severity.* Of those who do define the severity, a few authors tend to minimize the degree of swelling. The recent infarct is "generally somewhat swollen." (Buzzard and Greenfield,[11] p. 109), and "the element of pressure is, if not absent, at least trifling in degree" (Gowers,[25] p. 433). On the other hand, many authors have noted that the swelling may be marked,† and may be associated with evidence of increased intracranial pressure.‡

Sometimes, especially with occlusion of the internal carotid artery with massive encephalomalacia, usually in the distribution of the middle cerebral artery, this marked swelling is associated with clinical and pathologic evidence of transtentorial herniation.[6,22,23,38,55,60] Although similar cases of rapid death following sudden occlusion of the internal carotid artery with marked hemispheral edema have been noted by others,[30,48,65] no comment was made concerning transtentorial herniation. It is remarkable that many modern reviews of such cases either have minimized the evidence of increased intracranial pressure [3,4,61] or have not mentioned it.[37,68]

Starr [65] (p. 494) stated that "there are some cases of apoplexy in which the only lesion found after death is an oedematous state of one hemisphere. These are the cases in which a thrombosis of one internal carotid or middle cerebral has been followed by a rapidly fatal termination before softening has been produced." Gowers [25] (p. 437) recognized similar cases, but did not emphasize the swelling: "The symptoms of this extensive thrombosis are necessarily severe—hemiplegia with deepening coma and death at the end of (usually) 4 or 5 days." Hunt [33] described swelling of the cerebral convolutions but did not describe the position of the midline or evidence of transtentorial herniation in his Case 2 in which death occurred two days after traumatic occlusion of the carotid artery. The patient was unconscious, but the pupils were equal.

Hiller [30] (p. 314) noted that emboli to the internal carotid artery are soon fatal, with marked edema of the whole hemisphere. In a table on page 299 he recorded edema in 9 of 15 cases of embolism, but not in cases of cerebral hemorrhage or atherosclerosis; the duration and degree of swelling, however, are not recorded.

Of the many descriptions given, only a few particularly appropriate ones will be quoted.

1. Cobb [14] (pp. 141-142) emphasizes that "asphyxia at first causes a marked dilatation of the small vessels, their walls becoming more permeable and causing edema, and finally diapedesis of red cells takes place.

* References 7, 9, 15, 17, 25, 28, 34, 41, 47, 49, 65.

† References 16, 29, 30, 36, 50, 59, 66.

‡ References 2, 5, 13, 14, 18, 21, 26, 44-46, 56, 57, 63, 72.

. . . The infarct (if of considerable size) at first may give symptoms of increased intracranial pressure, because of the concomitant edema and surrounding congestion. If the patient survives this acute phase, the portion of brain actually ischemic degenerates."

2. Alexander [1] remarks that, in contrast with other types of edema, the edema in cerebral infarction involves the gray as well as the white matter.

3. Courville [15] (p. 129) succinctly summarizes the time course of encephalomalacia and distinguishes between the superficial and the deep portion of the lesion:

> During the first few days the margin of the area is made out only by a slight difference in consistency and by slight swelling of the involved convolutions. As time goes by, the swelling remains for several weeks, undoubtedly due to the presence of increased amounts of fluid in the decadent brain tissue. It is not often that one sees the lesion during this interval stage, and only when death is due to other causes.

4. Alpers [2] describes an area of recent encephalomalacia as follows (p. 466): "In large softening involving the cerebral hemispheres the tissue is swollen, soft to the palpating fingers and has a very edematous appearance when fresh. Chemical studies indicate that the brain in vascular occlusion is actually edematous." Further on (p. 468) he notes that in such cases "the cerebrospinal fluid may show an increase of pressure, especially during the acute cerebral episode, but it is rarely over 300 mm. of water."

5. More recently, in a study of occlusion of the internal carotid artery, Berry and Alpers [6] state (p. 234) that "the presence of brain swelling in the early course of the pathologic process is a well recognized consequence of the sudden occlusion of a vessel within the brain." In 15 of their 21 cases death occurred in 12 days or less, in 12 with swelling, in 10 with uncal herniation, and in 6 of these with pontine hemorrhage. Further data on these cases are given in Table 2.

Some estimates have been made of the time course of development of the swelling, but these have varied considerably. The time of onset has been said to be immediate (Oppenheim,[49] p. 519), within one [65] or a few hours,[47] within 12 to 18 hours,[20] "during a period of several days, probably between 2 and 7 days," [21] or "late." [25] "It builds up gradually so that at the beginning of the episode, the cerebrospinal fluid pressure may be normal and there may be no clinical evidence of increasing brain swelling. At the end of 24 hours, however, it is well developed. It probably attains its maximum on the 3rd or 4th day, and then subsides somewhat over the next 3 to 4 or 7 days" (Foley [24]). Other estimates of the duration of the swelling have also varied: a few hours or a few days,[43] at least 3 days,[18] at least 10 days,[20] 12 days,[6,19] and over 7 weeks.[57] Generally, however, authors have been content to refer simply to the "acute stage" or to some indefinite time "when the collateral circulation is established" (Starr,[65] p. 494). In monkeys maximal swelling occurred about the third day (Harvey and Rasmussen [27]) and disappeared by the 17th day; Petersen and Evans [51] noted swelling in the only monkey killed one day after clipping the middle cerebral artery.

As for other clinical correlates, some authors have considered swelling with encephalomalacia to be important only in the early clinical improvement, as the edema subsides (Brain,[8] p. 329; Wilson,[71] p. 1386). This is perhaps implied in other textbooks, in which the edema is described as occurring in the normal tissue surrounding the area of infarction (Merritt,[43] p. 163; Wechsler,[69] p. 341). No clinical correlate is suggested by Merritt,[43] but Wechsler [69] comments that coma in cases of cerebral embolism may "be very deep in the case of occlusion of a large vessel when cerebral anemia or edema are marked."

Merritt [43] provides several tables of interest, but, unfortunately, gives no estimate of the duration of the lesion when the various observations were made. In Table 42, p. 169,[43] pupillary dilation *on the side of the lesion* is recorded in only 3% of

cases of cerebral hemorrhage and in 4% of cases of thrombosis, and *on the side opposite to the lesion* in 30% of cases of hemorrhage and in 9% of cases of thrombosis. In Table 44, p. 170,[43] the cerebrospinal fluid pressure is noted to be over 200 mm. in 57% of cases with cerebral hemorrhage, in 22% with thrombosis, and in 10% with embolism. In Table 46, p. 175, the duration of life after onset of symptoms is seen to be almost equally distributed in the two intervals of 1 to 4 days and 5 to 14 days, 30% to 41% of patients dying in these intervals, regardless of cause (hemorrhage, thrombosis, or embolism).

B. Clinical Observations.—Examination of Tables 1 to 5 reveals many interesting clinical observations, some of which are not in agreement with certain of the opinions summarized in the above review of the literature.

Disturbances in sensorium were very common during the first few days. Of the 36 patients dying during the first week with specific information available, only 8 were recorded as being mentally clear, whereas 17 were comatose and the others were more or less stuporous. This may be merely an indication of the severity of the impendingly fatal lesion, but in the cases of death after longer durations, sensorial depression was also frequently noted to have been present during the first few days.

Fewer observations were recorded concerning the size of the pupils, but ipsilateral pupillary dilation was the most commonly recorded finding (eight cases). In two other cases ipsilateral constriction was followed by dilation of the pupil. Single cases had ipsilateral constriction, contralateral dilation, or bilateral pupillary dilation, respectively; only 6 patients dying during the first week were specifically noted as having had normal pupils. In the patients dying after longer durations, inequality of one or the other pupil was occasionally noted.

Papilledema was rare and usually slight, and the CSF pressure was usually within normal limits (18 cases), but in 7 cases it was measured as over 200 mm. during the first several days.

C. Clinicopathologic Correlations.—From the above observations of swelling of the infarct, transtentorial herniation, and shift of the midline, it is possible to account for only a part of the clinical picture: the delayed progressive decerebration with its effect on depth of coma, rigidity of the extremities, and changes in pupillary size, blood pressure, and pulse rate. It is not possible, however, to account for the sudden severe change in level of consciousness which often occurs immediately at the onset of the hemiplegia.

This contrast between the pathogenesis of coma at the onset and later has received little comment in the literature. Gowers[25] (p. 433) hinted at the problem, differentiating between the coma due to infarction and that due to hemorrhage, but he did not offer any satisfactory explanation. In discussing the mechanism of production of coma, he stated (p. 433)[25]:

> Coma lasting for 5 or 6 days may pass away when it is due to softening, but usually ends in death if due to hemorrhage. The mechanism by which apoplexy is produced by vascular obstruction scarcely can be altogether the same as in hemorrhage, since the element of pressure is, if not absent, at least trifling in degree and late in time, due only to the oedematous swelling which comes on after the onset.

Nielsen[48] also differentiated between cases with sudden catastrophic hemiplegia and cerebral edema and cases of sudden coma and death, but did not offer an explanation of the difference.

Several possibilities might be considered.

1. Is coma at onset a consequence of massive cortical damage, directly or indirectly through diaschisis or neural shock disrupting the function of lower structures? This effect might be more prominent if the lesion involved the dominant hemiphere. The facts that in some cases with damage to the dominant cerebral hemisphere coma does not develop and that in some cases of nondominant cerebral lesions coma does develop speak against both these suggestions.

2. Is coma at onset a consequence of simultaneous ischemia of subcortical structures, especially the midbrain, through insufficiency of the posterior communicating and posterior cerebral arteries? There is no good evidence for this theory, but it would seem plausible and compatible with all other observations. Variation in recovery of blood supply may also account for transient improvement in level of consciousness or for otherwise inexplicable and bizarre changes in pupillary size, blood pressure, and rate. Superimposed on this early ischemia of the midbrain may later appear evidence of transtentorial herniation, which would make it difficult at autopsy to recognize the previous lesion.

From the above morphologic and clinical considerations the following hypothesis concerning carotid and middle cerebral artery insufficiency is offered:

I. Sudden cerebral ischemia of a certain duration or severity may cause sudden hemiplegia and other neurological signs.

II. A. If the ischemia also involves the midbrain, coma and decerebrate phenomena may occur immediately.

B. If the ischemia is of brief duration, necrosis and swelling will be insignificant, and recovery should be reasonably prompt and complete.

C. If the ischemia is of sufficient duration, necrosis and swelling of the necrotic tissue will develop.

1. The swelling is proportional to the volume of tissue infarcted.

2. The time course of development and resolution of the swelling is defined by Figure 3.

(*a*) Transtentorial herniation occurs more rapidly than shift of the midline, and, if severe enough, may produce decerebration within the first few hours or days.

(1) More rapid absorption or displacement of cerebrospinal fluid may account for the relative ease with which transtentorial herniation may occur.

(2) Possibly slight differences of the order of a millimeter or so may account for marked differences in the clinical appearance of patients with transtentorial herniation.

(*b*) Greater swelling may be found than would be expected for the duration and may be accounted for by the superimposition of a recent massive cortical infarction upon an old small subcortical infarction, clinical signs of the separate episodes being masked because of the similarity of neural pathways involved.

(*c*) Less swelling may be found than would be expected for the duration and may be accounted for by bilateral infarction or may be interpreted as evidence that actual infarction was minimal and that clinical signs were due to transient physiologic dysfunction or to only selective neuronal necrosis.

Certain therapeutic considerations arise from the above hypothesis: One should be prepared to perform decompression of the brain within the first day or so following massive encephalomalacia.[60,63] In the monkey "a bony decompression of at least 3 cm. diameter was found necessary to prevent death of the animal from cerebral edema associated with the infarction."[54] Nielsen,[48] however, believed that "in the cases with sudden catastrophic hemiplegia and cerebral edema and in those with sudden coma and death it will make little difference whether the surgeon is called or not."

It is readily admitted that the differential diagnosis may be quite difficult between the massive lesion under consideration and the more frequent smaller lesions in which swelling would not be so significant. This is not the place to discuss the many and complicated aspects of various treatments, medical as well as surgical; but it would seem that internal decompression (e. g., removal of the infarcted tissue and/or of the herniated hippocampal formation) or massive external decompression would be of greater benefit than the usual, relatively small subtemporal decompression or medical attempts at dehydration. The recent experiments of Bulle,[10] however, suggest that reserpine may be of benefit in relieving cerebral edema produced by liberation of serotonin from thrombocytes, a new concept

with therapeutic implications beyond the more classical theory of increased capillary permeability following simple anoxia.[14,29,58]

From the above considerations of pathology and therapy, although some of the early clinical improvement following encephalomalacia may be attributed to subsidence of acute edema (Brain,[8] p. 329; Wilson,[71] p. 1386), emphasis might better be placed on the reverse of this statement, namely, that most of the early deaths are directly due to the acute swelling which occurs probably quite regularly with massive encephalomalacia.

Summary

From a review of the literature and a study of autopsied cases of sudden, massive, ischemic encephalomalacia due to occlusion of a major artery to the brain, it is concluded that swelling of the necrotic tissue develops rapidly and almost regularly. The temporal course of this swelling is presented in Figure 3. The swelling is manifest within the first day by swelling of the gray and white matter within the infarct and by transtentorial herniation of the ipsilateral uncus and hippocampal gyrus; transtentorial herniation may be severe enough to cause clinical signs, and even death due to decerebration. Swelling of the infarcted brain, as manifest by the shift of the midline, continutes to develop during the first three to five days, when it reaches a maximum. Deaths during the first week are usually directly related to this swelling. The swelling then subsides, disappearing after about two weeks, so that deaths after this period of time are generally due to extraneural complications, such as bronchopneumonia, pyelonephritis, and uremia.

Occasionally more or less swelling occurs than would be expected from the duration recorded; tentative explanations are offered in the nature of subsidiary hypotheses. Insufficient data are available to determine whether there is significantly more swelling with hemorrhagic infarction or infarction of even larger volumes of tissue, but the etiology of the infarction (thrombosis or embolism) and the age of the patient do not seem to be critical factors.

Therapeutic implications are briefly considered.

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Encephalopathies of Anoxia and Hypoglycemia

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Cerebral anoxia and hypoglycemia of varying severity and diverse causes commonly present neurological problems. Minor transient symptoms are readily diagnosed when they follow insulin injections or operation, but may escape recognition when due to less evident factors, such as hyperinsulinism or paroxysmal cardiac dysfunction. Severe cases with permanent cerebral damage are uncommon but are apt to occur as preventable clinical accidents. It is the purpose of this report to present some clinical and pathological data from a selected group of such severe cases.

As preliminary discussion, only brief reference can be made to the vast and scattered literature. The experimental study of anoxia is as old as the subject itself and was of much interest to the philosophers and savants of the 17th and 18th centuries, but the modern era may be said to date from Astley Cooper's [1] effort to determine the maximum time for which the brain could survive total deprivation of its blood supply. Many subsequent investigations of this type have been undertaken, notably those of Gildea and Cobb [2] and of Kabat and his colleagues.[3] Using dogs, they found that total arrest of the circulation to the brain for six minutes was regularly followed by complete recovery and that arrest for eight minutes resulted in permanent damage. In man it is usually held that two minutes is the maximum period of circulatory arrest from which complete recovery of neurological function may regularly be expected, although Meyer [4] has reported a case in which severe lesions followed cardiac arrest for one minute.

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The fundamental physiology and the classification of the anoxias were established by Haldane and Priestley [5] and by Barcroft.[6] Subsequent work has been based on their classical studies and has elaborated the circulatory and metabolic, as well as the respiratory, aspects of the subject. It was upon this extensive background of knowledge of anoxia that hypoglycemia became a relatively common clinical event and has come to be considered an example of histotoxic anoxia. The similarity of partial anoxia, hypoglycemia, and barbiturate intoxication was emphasized by Schmidt.[7] He measured the changes in mean blood pressure, arteriovenous oxygen difference, cerebral blood flow, oxygen uptake, and cerebral vascular resistance in partial anoxia, hypoglycemia of varying severity, and thiopental (Pentothal) anesthesia. The oxygen uptake of the brain is reduced in each of these states, and in all the circulatory responses are similar. The mean blood pressure falls; the cerebral blood flow rises; cerebral vascular resistance falls, and the arteriovenous oxygen difference falls.

In hypoglycemia the cerebral oxygen uptake falls pari passu with the fall in blood sugar, and many studies have emphasized its relationship to anoxia and have stressed that glucose is the only significant substrate for oxidation in the central nervous system.

"The multiplicity of the defense against hypoglycemia indicates the importance of preventing a fall in the blood sugar level . . . and this appears to be the essential function of the neuroendocrine balance of carbohydrate metabolism" (Himwich [8]).

In the event of abrupt failure to supply adequate amounts of either oxygen or glucose to the brain, there is little margin of safety, and a characteristic and similar se-

quence of changes appears in both conditions. The reported changes vary from massive hemorrhage to gliosis of the white matter without demyelination, and for many years symmetrical focal necrosis of the corpus striatum was thought to be the characteristic lesion of anoxia. It is relatively recently that the widespread degeneration and necrosis of nerve cells with corresponding glial proliferation have come to be recognized as characteristic. The changes are found typically in the cerebral cortex, particularly in Layers II, III, and IV, and in the striatum and cerebellum. Investigation of the oxygen consumption of various parts of the brain shows a striking correspondence between the area of greatest consumption and the areas most frequently damaged by anoxia and by hypoglycemia.

Outline of Case Material

Cases of severe anoxia and hypoglycemia admitted to the Toronto General Hospital and to Sunnybrook Hospital (Department of Veterans Affairs) in recent years, and the material available in the Department of Neuropathology, University of Toronto, have been reviewed. The cases of carbon monoxide asphyxia include practically all of those admitted to the Toronto General Hospital in a 10-year period, 1946-1955, and the figures are of some quantitative significance. The other cases of anoxia and hypoglycemia are selected examples of severe encephalopathy, and no attempt was made to determine the total numbers inclusive of milder cases.

Carbon Monoxide Poisoning.—These cases have been divided into five groups.

Dead on admission	5
Died with no recovery of consciousness	10
Recovery followed by relapse (1 fatal and 2 with permanent deficit)	3
Recovery with permanent deficit	6
Full recovery	61

From these figures it appears that, using the customary methods of treatment, including tracheotomy, of those patients, who are alive on arrival at hospital, 3 out of 4 will make a full recovery, 1 out of 10 will make a partial recovery, and about 1 out of 7 will die.

TABLE 1.—*Classification of Material*

Carbon monoxide asphyxia		85
Fatal	16	
Surviving	69	
Cardiac or respiratory arrest with anesthesia or surgery		9
Fatal	8	
Surviving	1	
Hypoglycemia		16
Fatal	11	
Surviving	5	

The neuropathological findings in those patients who were dead of arrival at hospital were congestion, edema, and scattered petechial hemorrhages in the cerebrum. In two cases early neuronal changes were noted in the thalamus, globus pallidus, and cerebral cortex.

Of the other fatal cases, five survived 2 days, two survived 4 days, and the others, 6, 8, and 10 days, respectively. Clinically they all showed profound disorders of consciousness, with the signs of "decortication," "decerebration," or complete unreactivity. At autopsy, edema was still present in those surviving two and

Fig. 1.—Carbon monoxide asphyxia with death in nine days. Extensive focal softening in globus pallidus.

four days, and the characteristic lesions were present in those cases of longer survival. Figure 1 shows bilateral softenings in the globus pallidus of a patient who survived nine days following carbon monoxide asphyxia.

The clinical sequence of recovery in those patients who survived without relapse, although of variable rate, is similar in all cases and may be arrested at any stage. An early deep coma, or state of unreactivity, gives way to a decerebrate condition of stupor and delirium and then a decorticate state with confusion and automatism, before recovery of the highest cerebral functions. Superimposed on this general pattern of recovery there occur an immense variety of focal symptoms, psychotic reactions, spatial disorientation, and motor disorders, such as hemiparesis, athetosis, or Parkinsonism. Frequently in the later stages of mild confusion or automatism, one can demonstrate agnosias, constructional apraxia, or dysphasia. Some of these points are illustrated by Cases 1, 2, and 3.

CASE 1.—*Carbon monoxide poisoning with residual dysphasia and hemiparesis.*

A., an 18-year-old girl, was deeply unconscious on admission to hospital. The eyes were deviated to the right. There was generalized muscular rigidity and twitching of the arms and legs. The pulse was 138 per minute, the respirations 30, and the temperature 103 F. Lumbar puncture revealed clear fluid under increased pressure. The veins of the optic fundi were full, but there was no papilledema. By the fourth day she was able to respond to simple commands, but on the sixth day the arms were spastic, the legs flaccid, and the plantar response down-going. On the seventh day the legs became increasingly spastic, the reflexes were hyperactive, and a bilateral Babinski response developed. Over the next four days the spasticity decreased and she steadily improved. At the time of discharge, two weeks after the accident, there was still increased tone in the limbs, with exaggerated reflexes, but the plantar responses were flexor. There was a severe, primarily motor, aphasia, which had become evident as normal consciousness was approached. She was last seen five years after the accident. She had married and had one child. Examination revealed considerable motor aphasia and extrapyramidal rigidity in the right arm and right side of the face. She had taught herself to write with the left hand.

Another case of survival with severe residual effects follows.

CASE 2.—*Carbon monoxide poisoning with residual Parkinsonism and dementia.*

B., a 24-year-old man, attempted suicide with carbon monoxide in his car. Concern about possible head injury led to ventriculography, which was normal. The initial few days of deep stupor were followed by many days of confusion with restless, noisy behavior. Gradually he resumed full consciousness after three to four weeks, and there evolved a more static picture of dementia with generalized muscular rigidity but little tremor. Three successive electroencephalographic tracings showed changes in keeping with the clinical effects. The first, taken nine days after the accident, reveals complete absence of normal frequencies with replacement by diffuse high-voltage slow waves. The second tracing, four months later, shows considerable improvement with return of alpha frequencies but many abnormal 3-6-second slow waves. A third tracing, at six months, shows further improvement, although there is a large amount of residual intermittent slow-wave abnormality. An air encephalogram, carried out four months after the accident, showed gross enlargement of the lateral ventricles. Five years after the event he remained confined to a mental hospital in a state of Parkinsonism and dementia.

CASE 3.—*Surprising late recovery from severe carbon monoxide encephalopathy.*

C., a 24-year-old woman, was admitted to hospital in deep coma following gas poisoning from a stove. There were repeated tonic seizures; breathing was labored, and a tracheotomy was required. She remained in deep coma for days and then passed into a muttering, resistive state for two to three weeks. For the next three weeks she was mute and unresponsive, with quadriparesis and bilateral extensor plantar responses. Six weeks later she showed some recovery of consciousness and movement but was confused and severely aphasic. Four months after exposure there had been much recovery; she was talking well and was discharged from hospital. She continued to improve in remarkable fashion, and by eight months there was only moderate hemiparesis and slight mental impairment.

These cases illustrate the instability of the clinical state and the corresponding difficulty of prognosis in the early stages. They also show the characteristic mixture of signs of diffuse and focal damage to the nervous system so common in these cases. Striking delayed improvement, as in Case 3, is not confined to recovery of intellectual function, for there are reports of cases in

which the manifestations of Parkinsonism disappeared months after gassing.

The final group of cases of carbon monoxide poisoning is made up of those in which early recovery was followed by relapse, which was sometimes fatal. Examples of such cases are Cases 4 and 5.

CASE 4.—*Temporary remission with fatal carbon monoxide poisoning.*

D., a 14-year-old youth, remained unconscious for a period of 48 hours after the accident. Thereafter he rapidly recovered consciousness and was able to speak to his father after 56 hours. On the fourth day his pulse became rapid, respirations were shallow, and the child lapsed again into unconsciousness, with cyanosis and falling blood pressure. Death occurred later that day, four days after the asphyxiation. Autopsy findings were normal except for the brain, which showed diffuse congestion and bilateral hemorrhagic softenings in the globus pallidus. This remarkable relapsing course is commoner with carbon monoxide than with other forms of anoxia.

CASE 5.—*Carbon monoxide asphyxia; remission followed by severe cerebral symptoms.*

E., a 27-year-old woman, was found in deep coma from carbon monoxide poisoning. She slowly recovered consciousness and by the fourth day was walking well, was talking normally, and was apparently fully recovered. She was discharged from hospital on the seventh day. The following morning she developed right hemiplegia and complete aphasia. When she was seen four months later, there was right hemiplegia with hemianesthesia, hemianopia, and severe dysphasia. Air encephalography showed gross enlargement of the left lateral ventricle. When last seen, 14 months after the accident, she remained severely aphasic, and the arm was totally paralyzed; she regained some power in the leg and was able to walk with a cane.

Clinically, such relapses seem always to follow severe poisoning, which does not, in other respects, follow an unusual course. At a time varying from several hours to two weeks after gassing, relapse occurs relatively abruptly, with the occurrence of alteration of consciousness, a variety of focal signs, and often a fatal outcome. Recovery, even though delayed, may be complete. There does not yet seem to be any way in which cases liable to relapse in this way can be distinguished from those in which recovery will be uninterrupted. It is to be noted that these cases do not resemble those of chronic carbon monoxide intoxication in the sense of prolonged exposure to low concentrations.

Anoxia Complicating Surgery and Anesthesia.—In this series there were nine cases of anoxia occurring as a complication of surgery and its attendant hazards. Eight cases were fatal, the earliest death occurring eight hours after the accident and the latest at nine weeks. Respiratory arrest, cardiac arrest, postoperative hypotension, and laryngeal spasm during intubation were among the several causes of anoxia. The operations varied from episiotomy to mitral

Fig. 2 (Case 6).—Anoxia from postoperative respiratory obstruction 10 days before death. Low-power view of the frontal cortex showing large numbers of fat-laden histiocytes in central laminae. Scarlet red stain.

commissurotomy, and a wide range of anesthetic agents was given. No useful statistics could be gleaned from this small series. We wish only to present two representative cases, with emphasis on the pathological findings.

CASE 6.—*Fatal anoxia from postoperative respiratory obstruction.**

F., a 48-year-old man, five days after subtotal thyroidectomy, developed complete laryngeal obstruction, which resulted in an estimated five minutes of complete anoxia. Thereafter he remained in coma with recurrent generalized clonic spasms until his death, 10 days later. Grossly the brain showed only congestion and edema. Microscopically, the most important changes were found in the cerebral cortex and the basal ganglia. Neuronal changes were everywhere most conspicuous. A low-power view of the full thickness of a section of precentral cortex is shown in Figure 2. The relative sparing of the subpial and the deeper layers is demonstrated, and the normal structure of the middle layers is completely replaced by masses of fat-laden histiocytes. Destruction of neurons was generally less marked in the fifth layer, but even here ghosts of neurons were seen in most places, with only an occasional cell which did not appear irretrievably damaged (Fig. 3). Figure 4 is a high-power view of the globus pallidus, revealing severe degeneration of all neurons.

Similar moderate to severe neuronal changes were also present in the putamen, the caudate, the thalamus, the superior colliculus and the Purkinje cells of the cerebellum. Cells in the lower brain stem showed little or no change.

The pattern of neuronal damage in this case is typical of the graded susceptibility alluded to above. This sequence was first carefully defined by Grenell [13] and was in essential agreement with the earlier work of Drinker.[14] The cells of the cerebral cortex are most susceptible, especially in Laminae III and IV. Little less vulnerable are the Purkinje cells of the cerebellum and the cells of the corpus striatum, followed by the sensory and internuncial cells in the brain stem. The larger motor cells in the brain stem and spinal cord are the most resistant. As with carbon monoxide asphyxia, survival for some days is necessary before the widespread changes can be seen. The next case illustrates additional pathological findings.

* Reported in full by Douglas [12] in 1949.

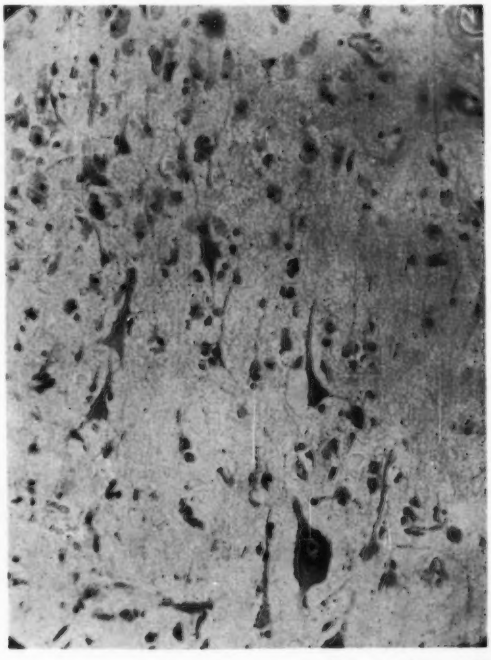


Fig. 3 (Case 6).—High-power view of Layers III and IV of the frontal cortex showing nerve-cell changes. Nissl stain.

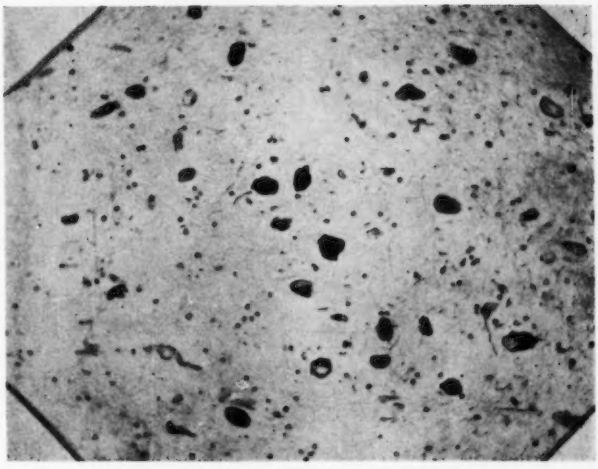


Fig. 4 (Case 6).—High-power view showing nerve-cell changes in pallidum. Hematoxylin-eosin stain.

CASE 7.—*Fatal cerebral anoxia from cardiac arrest.*

G., a 72-year-old man, developed cardiac arrest postoperatively (exact duration unknown) and remained in coma, unresponsive to all stimuli, until his death, nine weeks later. The brain showed huge areas of complete cortical necrosis, the extent of which can be gauged by Figure 5, a coronal section through the posterior portion of the frontal lobes. Microscopically, there was severe patchy necrosis throughout the cortex, involving particularly the middle laminae. There was also extensive demyelination in the subcortical white matter, a remarkable (and oft-ignored) consequence of anoxia from diverse causes, and, as stressed by Courville, a lesion seen only when the patient survives for a considerable time after the anoxic incident. Gliosis was not seen, and vascular changes were not conspicuous.

The frequency of these accidents of anesthesia and surgery is probably underestimated. Bedford[15] has emphasized their frequency in minor form in the surgery of the elderly, and Bourne[16] has recently discussed the incidence of syncope during dental anesthesia. It seems likely that minor untoward results of operations from these causes are more frequent than has been thought.

Fig. 5 (Case 7).—Anoxia with death after nine weeks. Frontal lobes showing gross thinning of cortex.

In the matter of diagnosis, air embolism may be overlooked and is particularly to be feared in operations upon the neck, particularly if the patient is in the sitting position. The clinical features are very similar to those of anoxia and are apt to be attributed to sudden excessive fall of blood pressure, which is the consequence of air embolus rather than the cause of the cerebral symptoms.

Hypoglycemic Encephalopathy.—This is the third group of cases in which we have been particularly interested. They are briefly listed in Table 2.

Ten cases were fatal, and four patients survived with neurological sequelae. In four of the six fatal cases following insulin

TABLE 2.—*Hypoglycemic Encephalopathy* (14 Cases)

Exogenous insulin	
Psychiatric insulin therapy	7 (6 fatal)
Insulin therapy in diabetes	5 (4 fatal)
Suicidal (probably)	2 (none fatal)
Endogenous insulin	
Islet-cell tumor	1 (fatal)
Addison's disease	1 (nonfatal)

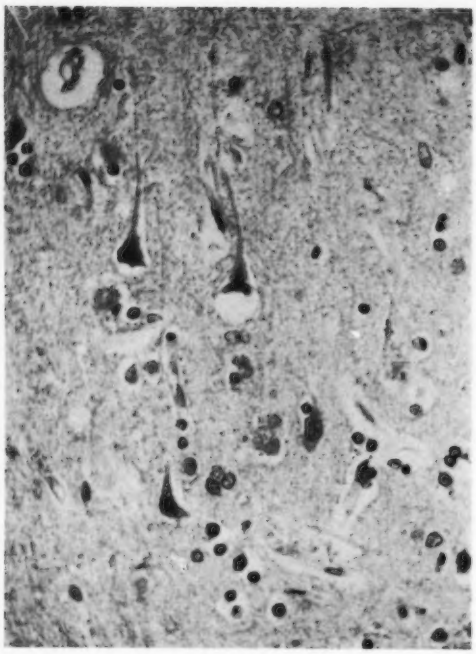


Fig. 6 (Case 8).—Precentral cortex showing homogenizing nerve-cell change. Hematoxylin-eosin stain.

therapy for mental illness, death occurred soon after a period of 1 to 12 hours of apparently normal health following treatment. In each case the brain showed marked edema and vascular congestion with herniation of the hippocampal unci or the cerebellar tonsils or both. There were no gross focal changes, and microscopic changes were slight or absent. The following case is briefly mentioned because the early neuronal changes were well shown.

CASE 8.—*Diabetic; fatal hypoglycemia after two days.*

H., a 63-year-old diabetic, developed so-called "irreversible" hypoglycemia and died after two days of coma. Figure 6 is a section of Lamina III, precentral gyrus. The cells are shrunken and triangular, with deeply stained nuclei and homogeneous eosinophilic cytoplasm. This "homogenizing nerve-cell change" is the commonest of the neuronal changes that are seen in anoxia of any cause.

CASE 9.—*Occipital laminar necrosis from hypoglycemia.*

I., a 57-year-old diabetic, postoperatively developed a fluctuating hemiplegia in association with recurrent hypoglycemia. A final episode of hemiplegia progressed to coma, and he died despite restoration of normal blood sugar levels. No lesion was found to explain the hemiplegia. There was, however, a localized area of softening

Fig. 7 (Case 9).—Hypoglycemia. Occipital cortex, laminar necrosis.

Fig. 8 (Case 10).—Hypoglycemic encephalopathy. Gross thinning of cortex seen best over insula on right side.

in the left occipital lobe, and section (Fig. 7) showed typical laminar necrosis of the cortex, visible even in the gross specimen.

The occipital, particularly the peristriate, cortex has often been described as a characteristic site of the lesions of severe anoxia and, according to Courville,[17] is seen most frequently in association with nitrous oxide anesthesia. To our knowledge, this patient did not suffer convulsive seizures or other complications which might have led to an anoxic interval, and it seems reasonable to assume that the change described may have been due to the hypoglycemia itself.

CASE 10.—*Islet-cell tumor; cerebral and spinal neuronal changes.*

There was one case of fatal hypoglycemia in association with islet-cell tumor of the pancreas. This case was previously reported in detail by Tom and Richardson,[18] particular attention being directed to the severe amyotrophy from extensive anterior-horn-cell destruction. This 33-year-old woman had suffered three attacks of unconsciousness in the year preceding her death. In the fourth attack, following a period of coma, she remained in a mute and severely demented state until her death, three months later. In addition to a clinical

Fig. 9 (Case 10).—Low-power view of temporal cortex, showing central laminar necrosis and gliosis. Hematoxylin-eosin stain.

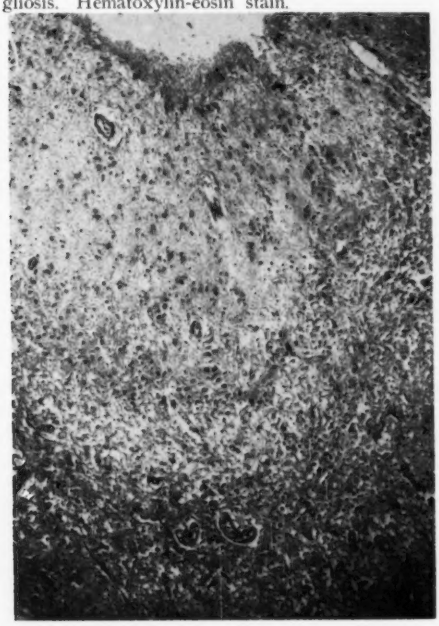


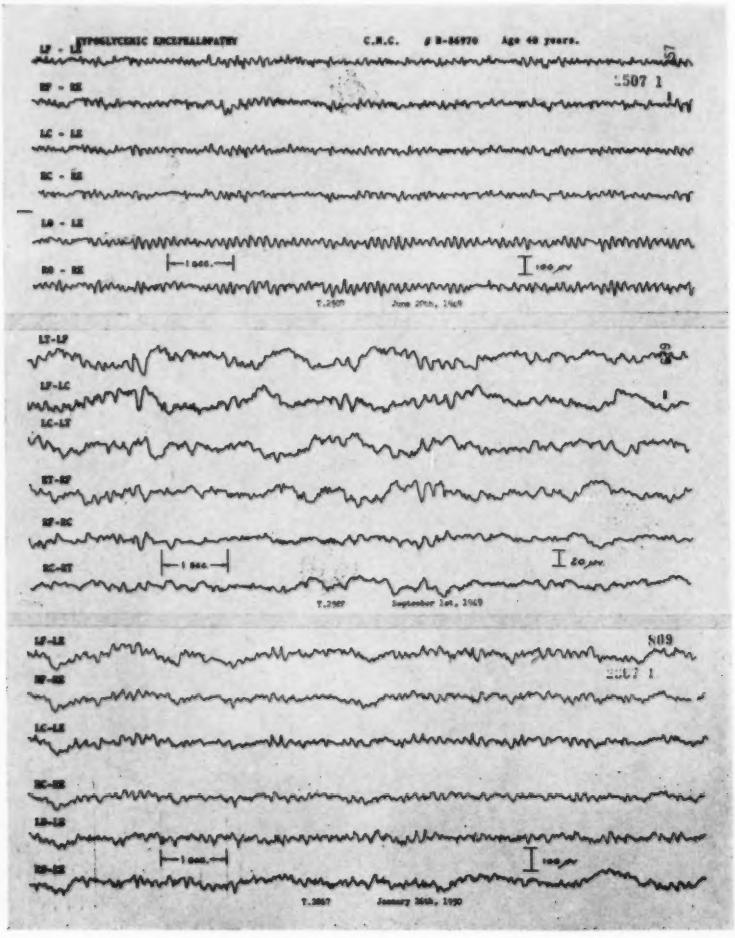
Fig. 10 (Case (10).—High-power view showing anterior-horn-cell changes. Nissl stain.

picture indicative of severe and diffuse cerebral damage, there was marked paralysis and wasting of typical lower-motor-neuron type in all limbs. At autopsy a benign islet-cell tumor was found in the tail of the pancreas. The brain was small, weighing only 1,170 gm. There were gross narrowing and softening of the right insular cortex and a palpable softening in the left temporal lobe. A horizontal section of the brain is shown in Figure 8. The narrowing of the cortical ribbon in the right insular cortex is well demonstrated. Figure 9 is a low-power view of the full thickness of cortex in the left temporal lobe. Destruction is virtually complete in the middle layers, with relative sparing of the subpial and deeper laminae. Figure 10, a high-power view in the ventral horn of the cervical enlargement, shows the usual feature of this case—the marked degeneration of the anterior horn cells. This was seen throughout the length of the cord and was responsible for the extensive muscular atrophy.

CASE 11.—*Severe cerebral damage from injected insulin.*

J., a 42-year-old man, accidentally received protamine zinc insulin, rather than soluble insulin, on eight successive days during psychiatric treatment. He lapsed into coma and remained in this state for three weeks. He then passed through stages of restlessness, then somnolence, to full consciousness in another three weeks. As consciousness returned, aphasia became obvious. There was mixed pyramidal and extrapyramidal hypertonicity

Fig. 11 (Case 11).—EEG tracings before, one month after, and six months after hypoglycemic incident.



in the right arm and leg, and a Parkinsonian tremor appeared in the right arm about six weeks after the accident. Although there was some improvement in subsequent weeks, comprehension remained grossly defective; there was considerable motor aphasia, and he was periodically restless and noisy. Figure 11 shows three representative electroencephalographic tracings. The first was taken prior to treatment and shows a normal tracing. The second tracing, one month after the accident, shows grossly abnormal electrical activity with slow waves in the 1-2-per-second and the 4-7-per-second ranges. The third tracing, six months later, shows considerable return of alpha frequencies and a much smaller component of abnormal slow waves.

The air encephalogram during this initial hospitalization showed moderate diffuse enlargement of the ventricular system. The dementia has persisted with little change in the subsequent years. Our last record of the patient was from Dr. Cline, Westminster Hospital (DVA), London, Ont., five years after the accident. At that time (1953) it was stated that he remained violent and abusive most of the time, with interludes of quieter dementia. The neurological examination otherwise showed only a generalized rigidity of extrapyramidal type.

CASE 12.—*Self-administered insulin; severe encephalopathy.*

K., a middle-aged diabetic, administered an overdose of insulin to herself, probably in a suicidal attempt. She had repeated right-sided convulsions for days, was grossly aphasic, and lay in bed repeatedly uttering several stereotyped phrases. For weeks one could not be sure that she had any contact with her environment. There was a right-sided hemiparesis and a Babinski response bilaterally. The electroencephalogram showed diffuse abnormality without localizing signs. Pneumoencephalography at 16 days showed early enlargement of the left lateral ventricle. Over the next month there was steady improvement in her clinical condition; she began to comprehend; speech became less stereotyped, and the hemiparesis improved. An air study 40 days after the onset showed marked progression in enlargement of the ventricles despite the steady clinical improvement. When she was last seen, two years later, there was marked residual receptive dysphasia and mild dementia.

CASE 13.—*Self-administered insulin with encephalopathy; diagnostic problem.*

L., a 21-year-old nurse, was found in a restless, semiconscious state. She shortly lapsed into unconsciousness, examination revealing only hypertonicity in all limbs and a bilateral Babinski response. The blood sugar was found to be 37 mg. %. It is of interest that the blood sugar test was suggested by the preceding lumbar puncture, with chance finding of a low CSF sugar of 17 mg. %. No evidence was ever found to suggest the diagnosis of islet-cell tumor, and there was a strong suspicion, although no proof, of self-administration of insulin. The clinical assessment was supplemented by serial electroencephalograms. On the second day there was a grossly abnormal record, especially in the left frontoparietal region. During the first 10 days the patient showed no clinical improvement. She was noisy, incontinent, and irrational. A left-sided Babinski response was present. On the 11th day she began to respond to commands and to speak a few words. She was in this state when another EEG was taken, on the 29th day. There was much less abnormal slow-wave activity, but it was a rather silent record, with suppression of normal frequencies and a suggestion of cortical destruction in the left frontotemporal area. Slowly speech returned, but her behavior remained childish. She was last seen 14 months after the hypoglycemic episode. Emotional instability was still marked, but she had actually returned to simple nursing chores under supervision. The electroencephalogram at that time showed further improvement, although there was still some abnormal activity on the left side. The record showed no appreciable change from that taken two months after the accident. The air encephalogram at 14 months showed the lateral ventricles to be at the upper limit of normal in size, the right being slightly larger than the left.

It is evident that these cases are similar to those of carbon monoxide poisoning and of anoxia associated with surgery, both clinically and pathologically. They, particularly the psychiatric cases, have offered the best opportunities for the study of the dissolution of neurological function to anoxia (and hypoglycemia). The most important, perhaps, of the associated problems in these cases is what it may be that determines the irreversibility of some cases of hypoglycemic coma. The hypoglycemic symptoms in cases of pancreatic islet-cell tumor have been discussed in greater detail in a previous report.[19]

Noteworthy in these cases of hypoglycemic encephalopathy is the delay between recovery from hypoglycemia and the onset of fatal relapse, in four of the six fatal cases. These relapses were not associated with a recurrence of hypoglycemia, and clinically they are very similar to the relaps-

ing cases of carbon monoxide poisoning. The period of remission before serious relapse has been shorter than in some of the carbon monoxide cases, but there is probably a common explanation. We have not been able to find records of a case of hypoglycemia with relapse after so long a delay as may occur in carbon monoxide poisoning.

Comment

As others have pointed out, the cerebral lesions of acute carbon monoxide poisoning, of cardiac or respiratory arrest, and of hypoglycemia are the same in type and distribution. There are differences of emphasis among them; for example, necrosis of the globus pallidus is apt to be more massive and frequent after carbon monoxide poisoning, but this feature is by no means invariable and in other series[20] has been absent as often as present. It has frequently been reported as the result of anoxia of other origin.

Clinically the syndromes that result from these processes are similar. The picture consists of a diffuse disorder of cerebral function, reversible in whole or in part, with associated signs of focal damage to the nervous system, which are apt to be more persistent. As a rule, the onset of the encephalopathy is abrupt; the change in consciousness dominates the clinical picture, and the symptoms of focal damage appear during recovery. When the onset is less abrupt, as in hypoglycemia, the focal signs may be the initial event. Focal or generalized seizures are common in the acute stages, and less frequent as chronic effects unless associated with other clinical evidence of cerebral damage.

The electroencephalographic changes parallel the clinical findings. In the early stages diffuse bilateral delta waves appear, and in the stages of recovery focal, medium- and high-voltage slow waves, paroxysmal or continuous, are seen. In many cases serial air studies show enlargement of the ventricles, progressing rapidly in the early stages, and often concurrently with clinical improvement. Asymmetrical dilatation may occur appropriate to the focal signs when these are present.

The diffuse cerebral disorder and disturbance of consciousness appear to be better correlated with widespread sudden cortical damage than with any local injury, such as that, for example, to the reticular substance of the brain stem. The focal symptoms may usually, but not always, be related to definite focal lesions.

Very similar clinical syndromes are seen in other conditions which produce sudden cerebral damage. The commonest is probably closed head injury with cerebral concussion and contusion, aptly termed acute traumatic encephalopathy. Other conditions characterized by diffuse and focal cerebral damage are acute disseminated encephalomyelitis, hypertensive encephalopathy, and allergic and other toxic encephalopathies.

While the main features of the clinical and pathological findings may be explained in terms of the varied neuronal susceptibility of different parts of the brain to anoxia, the abruptness and severity of the anoxia, and the length of survival, there are a number of features that are less readily explained. First, there is the instability of the clinical state in the acute phase, during which the signs may vary considerably from hour to hour. In part this may be explained by variation in the degree of obstruction to the airway, but our impression is that this does not account for all the phenomena observed.

Signs of focal damage to the nervous system are usually seen in the stage of recovery but sometimes, particularly in hypoglycemia, appear in the early stages. This was present in three of our cases. It is apt to lead to error in diagnosis and to delay in the institution of appropriate treatment. An attractive explanation is to suppose that the area of brain whose function is disturbed early is more vulnerable than the rest by virtue of some predisposing cause, such as stenosis of its supplying vessel with or without a congenital anomaly of the

circle of Willis. The maximum possible blood supply to such an area would be less than it should be, and it might be expected to show symptoms of dysfunction sooner than areas with a normal vasculature. That such a sequence of events may occur has been demonstrated in the monkey by the induction of hypoglycemia after ligation of one middle cerebral artery (Meyer and Portnoy [21]). Two patients with hypoglycemic encephalopathy who had presented with such focal signs died. Post mortem, the intra- and extracranial vessels were seen to be entirely normal in one case, and in the other were normal except for a very thin posterior communicating artery on the side of the responsible lesion. While, therefore, such a mechanism may operate in some cases, it is not responsible for these focal signs in all.

The presence of severe cerebral edema in all cases of death in the acute stages of anoxia from whatever cause is apparently invariable. Its relation to the clinical and pathological findings is less definite. An indication that it may be related to the duration of unconsciousness is to be found in a recent report,[22] in which dehydration therapy with intravenous sucrose was followed by recovery of consciousness, a sequence which was repeated. It is possible that the edema of the acute stage, if maintained, may underlie some of the lesions, particularly those of the white matter, that may be found in anoxic encephalopathy. Patchy demyelination has been emphasized by Courville [23] to be a characteristic lesion in those cases in which an anoxic episode is survived for a period. It is known that cerebral edema may be followed by demyelination, and Jacob [24] attributed the white-matter lesions of anoxia to edema. In his view they were characteristically found in cases which showed a latent period, but this does not seem to be invariable.

The cases in which relapse occurs after apparent recovery, which may be clinically almost complete, are the most puzzling. They have been reported after anoxia of varied origin. These relapses are often attributed to vascular factors, the nature and mechanism of which have not been established, nor is it necessarily true that they all have the same pathogenesis. In Case 1, the bilateral symmetrical necrosis of the globus pallidus, which resulted in the patient's fatal relapse, is difficult to account for on a purely vascular basis. In other cases asymmetrical focal lesions occur in which a local vascular mechanism is more plausible. A delayed onset of Parkinsonism or of other focal cerebral symptoms may have different explanations. In the cases here described there would seem to be a better prognosis with CO poisoning than with anoxia and hypoglycemia of other causes. However, this difference is probably not real, and the ultimate results would be comparable only if we had included milder cases of hypoglycemia and anoxia of all varieties.

It is difficult to ascertain whether the same is true for the surgical cases. The incidence of episodes of cerebral anoxia is likely, according to Bourne, to be higher than has been thought, and in many of these less obtusive cases death does not occur. Such cases increase the number of patients whose disability may be laid to the door of avoidable cerebral anoxia, particularly in the elderly.

As regards treatment, the usual methods have been employed to ensure an adequate blood supply to the brain and a sufficiency of oxygen in the inspired air. In later years, tracheotomy has been done with increasing frequency soon after the patient is seen, and difficulty with the airway has been correspondingly reduced. The patients in this series were not treated for cerebral edema. Published reports and experience with a few subsequent cases suggest that it is likely to be a useful auxiliary measure. Nothing, it should be emphasized, can replace prompt and efficient "first-aid" measures if the disastrous consequences of anoxia and hypoglycemia are to be avoided.

Summary

Clinical and pathological findings are presented from selected cases of severe brain damage from anoxia and hypoglycemia.

With only minor individual variations, the clinical and pathological changes were essentially the same with carbon monoxide asphyxiation, anoxia from cardiac arrest, and severe hypoglycemia from hyperinsulinism. Severe permanent brain damage may result from all such causes, and the predominant effects are in cerebral cortex and basal ganglia.

The clinical picture of acute anoxic and hypoglycemic encephalopathy is discussed in detail. There is a pattern of diffuse cerebral arrest which is more reversible and an admixture of focal cerebral damage which is more permanent. A similar syndrome of acute encephalopathy may occur with various other conditions, such as trauma and encephalitis.

This common pattern of severe encephalopathy featured by initial deep unconsciousness is emphasized in the material here reported. It must be stressed that anoxia, particularly hypoglycemia, may produce focal cerebral symptoms, such as paresis or dysphasia, with no obvious diffuse cerebral disturbance.

Brief mention is made of the vital and practical implications. Many of these tragic cases of severe cerebral anoxia and hypoglycemia can be prevented by accurate diagnosis and by measures such as careful attention to adequate airway in unconscious patients.

170 St. George St.

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Metastases of Cancer to Primary Intracranial Tumor

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Introduction

The occurrence of multiple primary tumors in one patient has been noted frequently and is no longer considered remarkable. However, metastasis of cancer to another primary tumor is distinctly uncommon. Only five previous instances of metastasis to primary intracranial tumors have been reported. Osterberg [1] found three cases of metastatic carcinoma in meningioma; in two the metastasis originated from a primary site in the breast, and in one, from the bronchus. He added two cases. One patient was a 51-year-old white man with symptoms of a brain tumor. At craniotomy a meningioma was removed, which on microscopic examination contained large clear cells. The diagnosis was renal-cell carcinoma metastatic to a meningioma; this could not be confirmed by further clinical study, and autopsy was not permitted. The second patient was a 71-year-old white man who died of bronchogenic carcinoma with widespread metastases. At autopsy an incidental parasagittal meningioma was found, and histologic study showed metastatic carcinoma.

While these circumstances seem to represent a pathologic oddity, it is conceivable that the events may attain clinical significance in some cases. The metastasis may be responsible for sudden enlargement of the independent, slow-growing host tumor due to edema or hemorrhage or more rapid relative growth of the metastatic focus, producing acute onset or exacerbation of neurologic symptoms. In patients with clinically diagnosed malignancies, the surgeon may fail to operate upon resectable lesions, such as a meningioma, under the mistaken impression that this represents only a brain metastasis. However, recently there has been a greater tendency toward removal of symptomatic brain metastases to permit longer and more comfortable life, even though the patient is known to have spread of tumor elsewhere. With the increased number of such operations, it is likely that more instances of metastases to primary intracranial tumors will be discovered. Occasionally the microscopic examination may be the first indication of the presence of carcinoma elsewhere in the body, and the pathologist may be able to suggest its location, as in the case reported by Osterberg.[1]

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Report of a Case

A 73-year-old white woman was admitted for the first time to the Bronx Municipal Hospital Center in May, 1957, complaining of a lump in the right breast, diminished hearing with buzzing in the left ear, and "twisting" of the left side of the face. About five years previously the patient first noticed decreased auditory acuity in the left ear with a buzzing sound in this ear. For the past two or three years the patient had noticed a "twisting" of the face to the left side, accompanied by excessive tearing of the left eye, which had been slowly progressive, so that at the time of admission the patient could not move the left side of her face or forehead. She had also been unsteady on her feet for at least six months and had had an intermittent tingling discomfort radiating from the left upper gum area to the cheek, with pain around and beneath the left eye.

Three years before the patient had first noted a small, hard mass in the upper inner quadrant of the right breast after trauma. Four months prior to admission she fell and hurt this breast, and since that time the breast had been painful and the mass had increased in size and hardness.

On physical examination the significant findings were a fixed hard mass in the medial upper quadrant of the right breast with a large mass in

the right axilla. Neurologic examination revealed ptosis of the left eyelid, marked left-sided facial paresis, and hypesthesia to touch and pinprick over the left anterior surface of the tongue and the left cornea.

A needle biopsy of the breast mass revealed infiltrating carcinoma with scirrhous reaction. Special skull x-rays showed a slight rarefaction of the superior portion of the left petrous bone, close to the inner aspect of the internal auditory canal. Audiometric studies revealed primary left-sided hearing loss, probably retrocochlear in nature. The clinical diagnosis was carcinoma of the right breast with axillary metastases and neuroma of the eighth cranial nerve. The patient was treated with a total dose of 8,400 r to her right breast and axilla during a three-month period, with some regression of the breast mass.

The patient was readmitted several months after completion of the course of radiation therapy, because of left-sided weakness, of sudden onset. Physical examination revealed left hemiplegia, as well as the masses in the right breast and axilla. Chest x-ray showed many various-sized areas of increased density in the right lung, not previously seen. The clinical impression was embolic occlusion of the right middle cerebral artery, possibly due to tumor, with cerebral infarction. The patient was given 2,100 mg. of testosterone over a three-month period. The subsequent course was progressively downhill, and the patient was in coma for the last six weeks of life. During this time there was 3+ proteinuria, increasing generalized edema, and hypalbuminemia. The final clinical diagnosis was terminal widespread carcinoma of the breast, acoustic neurinoma, and nephrotic syndrome.

Only the pertinent autopsy findings are given here. The right breast contained a mass which measured 2×1.5×1 cm. and was hard, irregular, and nonencapsulated, with invasion and fixation of the adjacent fat. Metastatic tumor was found in the right axillary lymph node and several mediastinal lymph nodes. No tumor was present in the parenchyma of the left lung, but there were small discrete tumor nodules on the anterior left pleural surface, as well as along the course of both internal mammary vessels and on the anterior surface of the pericardium. The right lung was emphysematous and contained many rounded nodular masses of tumor within the parenchyma and on the pleural surface. The liver was not enlarged (1,350 gm.) and contained a few small (0.5-1 cm.) white tumor nodules near its surface. The kidneys were enlarged (180 gm.), pale, and firm; the cortices were swollen. The uterus had a small white tumor nodule in the cervix. The vertebral column showed yellow-white tumor irregularly infiltrating the body of the fourth lumbar vertebra.

There was an epidural mass in the region of the petrous portion of the left temporal bone, arising from the eighth cranial nerve, extending down toward the internal ear, and infringing upon the left temporal lobe. The internal aspect of the dura showed the surface to be intact throughout, with a gray-white, shiny appearance. This nodule measured 3×2.6×1.8 cm. It was well defined and apparently encapsulated, with some prominent vessels visible on the surface. It was separated from the attached dura by thin fibrous tissue, apparently representing capsule. The external aspect was grossly lobulated and bosselated, with a gray-tan color in the fixed state. The cut section was resilient and lobulated, with a faint whorled pattern. Within the parenchyma of this tumor was a well-defined, but not encapsulated, oval area, which measured 0.9×0.7×0.5 cm. It presented an opaque, dry, white-and-black variegated appearance and extended to within 2 mm. of the surface of the above-described nodule at the site of attachment to the dura (Fig. 1). The right hemisphere of the brain contained a tumor mass (4×4×3 cm.), poorly demarcated from surrounding cerebral tissue, with necrotic cystic and hemorrhagic areas, which involved the posterior half of the basal ganglia and extended to involve the cerebral peduncle. Another small, irregular metastatic tumor mass (0.5 cm.) was present in the gray matter of the left frontal lobe.

Microscopically, the right breast, right axillary and mediastinal lymph nodes, right lung, cervix, and brain all showed infiltrating carcinoma of similar histologic character, with cords and clusters

Fig. 1.—Gross photograph of cut surface of acoustic neuroma, showing area of metastatic carcinoma containing zones of hemorrhage. Background tissue is the loosely adherent dura.

Fig. 2.—Photomicrograph of section shown in Figure 1. Hematoxylin and eosin; × 25.

of tumor cells, as seen in duct carcinoma of the breast, extending through a dense fibrous stroma. There was widespread amyloidosis of moderate degree of the adrenals and kidneys, and less severe involvement of the arteries of the heart, liver, and spleen. The epidural tumor arising from the area of the eighth nerve was seen to be composed of masses of wavy, flowing cells in a somewhat whorled pattern, with some palisading of the nuclei. This tumor contained a single zone of metastatic carcinoma (identical with the metastatic carcinoma elsewhere) in sheets and clumps of solid cells, with areas of hemorrhage present. This combination was diagnosed as an acoustic neurinoma containing metastatic carcinoma from a primary breast focus (Fig. 3).

Comment

A review of the literature indicates the infrequent metastasis of cancer to cancer. When this does occur, certain neoplasms are most frequently involved; a number of explanations have been offered. The metastatic tumors most frequently involved are common neoplasms which characteristically show widespread dissemination throughout the body, such as primary carcinomas of the lung, breast, and prostate.[2] These neoplasms spread to organs which are often the site of independent tumors. Thus, bronchogenic carcinoma involves the adrenals, where adenomas occur frequently. Furthermore, the two tumors are so different in gross and histologic appearance as to permit easy distinction of the two lesions.[2] Thus, metastatic carcinoma in adenomas of the adrenal and in clear-cell carcinoma of the kidneys are easily discovered and diagnosed.

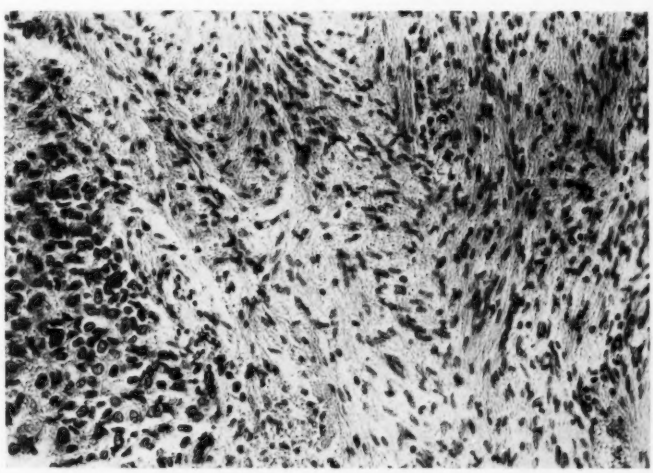

Fig. 3.—Photomicrograph of acoustic neuroma, illustrating the wavy-bundle pattern with palisading of nuclei and area of metastatic carcinoma from breast in one area. Hematoxylin and eosin; × 250.

The situation is not confused by the occurrence of histologic variants of the same primary cancer, such as bronchogenic carcinoma with both squamous and glandular features. Willis[4] has suggested that the high content of lipid present in clear-cell carcinomas of the kidney and the adrenal cortex may permit the preferential growth of metastatic tumor at these sites. Many of the host sites may not have been true neoplasms[2]; ovarian cysts, involutionary or inflammatory nodules of the thyroid, and hyperplastic areas of the adrenal are examples. The thyroid and adrenal were very common sites of metastases. The prominently rich vascular supply has been used to account for the frequency of hypernephroma,[3] as well as of thyroid and adrenal adenomas, as the host tumor.[2] Rabson[3] has suggested that cancer which destroys the host tissues of the body similarly may destroy any cells that come within its reach, including metastatic cancer cells from another primary site.

Rabson[3] could not estimate the statistical probability that the occurrence was pure chance because of the ill-defined and too numerous variables involved. Osterberg[1] considered that his cases were due to chance. An interesting observation[2,3] is that of the accepted cases of metastatic cancer to cancer; the host neoplasm itself failed to produce metastases in all but five cases.

Summary and Conclusions

A patient with clinical evidence of an acoustic neuroma and carcinoma of the breast is described. At autopsy metastatic carcinoma was identified grossly and microscopically within the acoustic neuroma.

Five previously reported instances of metastases of cancer to meningioma are noted. The literature concerned with metastases of cancer to cancer is reviewed. Explanations for such occurrences are noted, and the clinical significance is indicated.

The gross and microscopic photographs were by Mr. Milton Kurtz.

Albert Einstein School of Medicine, Eastchester Rd. & Morris Park Ave. (61).

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Protracted Coma from Delayed Thrombosis of Basilar Artery Following Electrical Injury

Clinicopathological Report of a Case

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Prolongation of life for more than a year after massive encephalomalacia involving the reticular activating substance of the brain stem with an essentially integral cerebral cortex in itself must be an exceptional occurrence. In the case under consideration the patient's collapse followed accidental exposure to a high-voltage electrical current after 19 days during which some personality change was observed. Necropsy revealed occlusion of the basilar artery. This sequence of events raises the question of how much such electrical injury contributed to the subsequent development of an occluding thrombus.

Report of Case

A previously well 45-year-old maintenance man suffered an electrical shock on June 20, 1955, while working on a high-voltage electrical switch box. The sudden flash of lightning temporarily blinded him; he complained of blurred vision, dizziness, and headaches and consulted a physician who made a diagnosis of thermal blepharitis and conjunctivitis. However, the patient was able to stay on his job until July 8, 1955. His family noted a distinct change in his personality. He no longer participated as formerly in his domestic life and wanted to be left alone. In contrast to his usual energy and self-willed determination, he appeared quiet, passive, and docile, "as though his will had been broken." In the early morning hours of July 9 the patient got up for a drink of water and suddenly fell to the floor; his right side was paralyzed, and a short while later he became unconscious and remained in deep coma until his death, on June 22, 1956, one year and two days after the accident.

On admission to the American Hospital on the night of his "stroke," his temperature was 99 F, pulse 88, respirations 20, and blood pressure 130/80. There were 5,500,000 red cells and 17,650 white cells per cubic millimeter, with 18% lymphocytes and 4% "stab" cells. During the first days in the hospital the temperature rose to 104.8 F, when the sedimentation rate was 48 mm. in one hour. Two spinal taps yielded bloody fluid, but a third puncture, on July 14, yielded a clear fluid under 250 mm. of water pressure with 3 cells per cubic millimeter, a negative colloidal gold curve, and 60 mg. of total protein per 100 cc.

On July 15, when one of us (E. H.) saw him in consultation, he appeared like a person resting in sound sleep, with a relaxed facial expression, rosy color, and easy breathing. There was no stiffness of the neck. The pupils were round and equal and did not react to light; corneal reflexes were present, though not brisk. The optic discs showed slightly blurred margins but no papilledema. The face was symmetrical. When one touched his lips, the patient responded by pouting them, as in an abortive sucking reflex. The arms and legs were paralyzed, with the hands held slightly flexed and the right leg turned outward with the foot supinated. The abdominal reflexes were absent, cremasteric reflexes diminished, and patellar and Achilles jerks present. A Babinski sign could be elicited on the right. There was no response to painful stimuli except to pricking of the nasal mucosa. The clinical diagnosis (E. H.) was that of an encephalopathy mainly involving the midbrain and the brain stem, quite likely resulting from an electrical-shock injury to the brain.

Dr. Joshua Spiegel, a neurosurgical consultant, who saw him on Aug. 13, confirmed the clinical findings, but, on reexamination on Aug. 25, found some decerebrate phenomena, such as rigidity and the Magnus and de Kleijn reflexes. His final impression was that of a pontine lesion, either thrombotic or hemorrhagic, on the basis of electrical injury to the basilar artery.

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From the Department of Neurology and Neurological Surgery, University of Illinois College of Medicine (Dr. Haase), and the Department of Nervous and Mental Diseases, Stritch School of Medicine of Loyola University and the Cook County Hospital (Dr. Luhan).

On Aug. 26 the patient was transferred to Cook County Hospital, on the service of Dr. Irving Sherman. His rectal temperature was 103.7 F, pulse 110, respiration 28 to 30, and blood pressure 130/100. Spinal fluid examination revealed a clear fluid under 120 mm. of water pressure, with 2 lymphocytes per cubic millimeter, total protein of 172 mg. per 100 cc., and 46 mg. of glucose per 100 cc. The Wassermann reaction of the spinal fluid (0.5 cc. of fluid) was negative.

On Sept. 2, the patient's condition was described as that of deep stupor. His eyes were tightly closed; his extremities stiffly extended. Magnus and de Kleijn tonic neck reflexes were not elicitable. The right side was more rigid than the left. The pupils were 4 mm. in diameter and fixed. The plantar reflexes were absent, but there was a bilateral Brissaud sign. The face perspired freely. On painful stimuli he moved his left extremities and head. The patellar reflexes were fairly brisk; the other tendon reflexes were decreased.

A month later urinary-tract infection with high fever supervened, which was successfully combated with antibiotics, and a severe diarrhea occurred, which was controlled by chloramphenicol, but later recurred.

On Aug. 29, 1955, an electroencephalogram revealed basic frequency of 6 per second with frequent bursts of right focal slowing, primarily in the temporal and frontal leads, with hemisphere spread. On Dec. 6, 1955, and Feb. 21, 1956, electroencephalographic studies showed basic 6- to 8-per-second frequency with some low voltage. There was irregular slow activity in all areas but no reliable focus. The patient was blinking.

On Feb. 23, pneumoencephalography was performed. The ventricular system was well visualized, and no abnormalities were seen. The sella turcica appeared normal. The falx was calcified.

The patient was tube-fed throughout his hospital stay, and aspiration of throat secretions was frequently practiced. In May, 1956, signs of aspiration pneumonia developed; the temperature rose to 105 F and the pulse rate to 150; respirations were 24 per minute, and the blood pressure was 90/70. The urine was loaded with pus cells. The fever receded under treatment with chloramphenicol.

On June 20, 1956, an entry in the chart by Dr. Irving Sherman describes the patient's steadily failing condition:

"Patient unconscious. Cough reflex present. Numerous decubitus ulcers on back and buttocks. Edema of distal parts of extremities. Marked wasting of all muscles. No spontaneous movements. The eyes were closed, but there is blinking of lids. A constant myoclonus of the palate at a rate of 120 per minute, and some lip movement can be seen. Pupils were round and equal. There was no spasticity, and no tendon reflexes could be elicited except feeble elbow reflexes. No pathological reflexes. Abdominal and cremasteric reflexes absent. No response to supraorbital pressure. No attempt at swallowing."

Dr. Sherman's impression was that of high brain-stem damage, which, in view of the history, he would relate to the electrical injury.

The patient died of cardiac failure two days later, on June 22, 1956.

Postmortem Findings

This was a coroner's case, and we are indebted to Dr. Alvin F. Bates, of the Cook County coroner's staff, for the general necropsy findings, and for making pathological material available for histologic study. The spinal cord was not examined.

General Autopsy.—The general necropsy findings, apart from the changes in the brain, were myofibrosis and eccentric hypertrophy of the heart; evidence of congestive failure, shown by chronic passive congestion of the liver, kidneys, and spleen, and bilateral hydrothorax. The aorta was not remarkable, whereas there was some intimal thickening of the coronary vessels. The lungs were edematous, and the kidneys showed arteriolonephrosclerosis.

Brain.—Gross Pathology: There was marked cerebral arteriosclerosis, confined largely to the vertebral-basilar system. The left vertebral artery was larger than the right, the lumina of the two arteries being 15 and 4 mm., respectively. The middle portion of the basilar artery was the site of an ancient thrombus. The basilar artery was 28 mm. long; the distal 9 mm. appeared as an empty, shriveled tube, while the middle 9 mm. was completely occluded by a firm, yellowish-gray clot. The superior cerebellar arteries on each side were patent and not collapsed; on the left, the superior cerebellar was represented by a pair of vessels. The beginnings of the posterior cerebral arteries appeared relatively collapsed and the posterior communicating vessels were small, but it would seem that some circulation was maintained in the posterior cerebral and superior cerebellar arteries through these posterior communicating vessels.

When the brain stem and cerebellum were separated from the rest of the brain by a cut through the cerebral peduncles, an extensive cavitation was revealed in the midline, which reached from the moderately dilated aqueduct through the central portion of the tegmentum, more pronounced on the left, and into the basis pedunculi, bilaterally, particularly on the right (Fig. 1).

The external surface of the brain appeared relatively normal except for evidence of mild cerebral edema; the leptomeninges were clear, and no visible or palpable areas of cortical softening were detected.

Fig. 1.—Section through the caudal mesencephalon, revealing extensive cavitation from old softening in midline structures, from the aqueduct through the central tegmentum and into the bases pedunculorum.

Serial coronal slices through the cerebral hemispheres revealed old anemic softening in the thalami, considerably more extensive on the left side, where the destructive process extended rostrally into the anterior thalamic nucleus and caudally into the pulvinar, whereas on the right side it was confined to the middle third of the nucleus, cutting a path through the medial nucleus to the third ventricle (Fig. 2). In a section through the posterior commissure, the softening involved the periventricular gray matter, the midbrain tegmentum, and the left pulvinar.

There was moderate dilatation of the third ventricle with some atrophy of the periventricular hypothalamic substance. The midbrain tegmentum remaining in the coronal slices had been destroyed by anemic encephalomalacia.

Transverse sectioning of the brain stem disclosed extensive ancient encephalomalacia, involving most of the basis and much of the central tegmentum of the rostral one-half to two-thirds of the pons. The caudal third of the pons, all of the medulla, and the cerebellum seemed macroscopically intact, but some atrophy was indicated by a slightly enlarged fourth ventricle.

Microscopic Examination: Sections through various portions of the cerebral cortex revealed edema of the leptomeninges, slight proliferation of glia in the first, or subpial, layers here and there, regular cytoarchitecture, and no infiltrative inflammatory change or demyelination, except in the region of the right visual cortex.

The left visual cortex showed edema of the leptomeninges, arteriosclerotic changes in the meninges and cortex, widening of the sulci compatible with some cortical atrophy, marked perivascular shrinkage spaces but no gross disturbance of cytoarchitectural pattern, and no demyelination.

The right visual cortex, on the other hand, disclosed an area of old partial softening with foci of more recent encephalomalacia (shown by accumulation of polymorphonuclear leukocytes in the necrotic foci).

In the basal ganglia near the gross softenings were some small arteries showing calcification of the media.

The softenings in the midbrain involved not only periaqueductal gray matter but also the tegmental reticular formation. Sections through the pons showed extensive encephalomalacia of the basis pontis, extending dorsally into the central pontine tegmentum to the floor of the fourth ventricle,

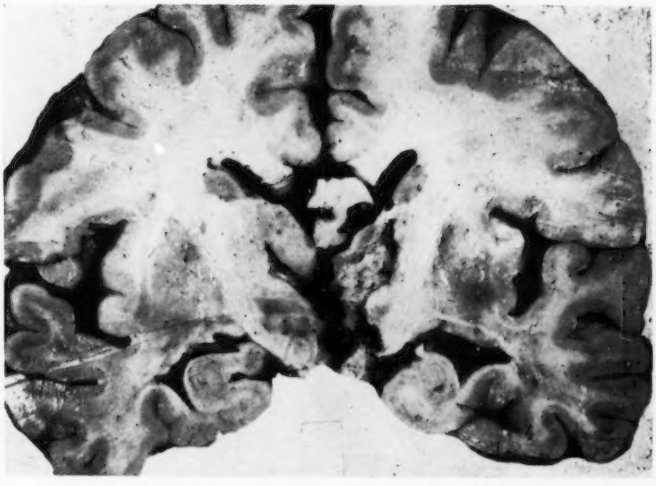

Fig. 2. — Coronal section of formalin-fixed brain, revealing encephalomalacia in thalami, more extensive on the left.

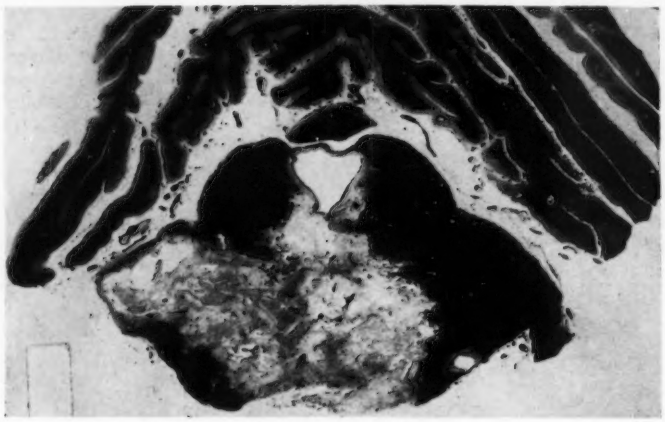

Fig. 3.—Rostral pons, showing effects of extensive softening. Note relative sparing of brachia conjunctiva. Weil stain.

rostral to the level of the entering trigeminal nerves. (Fig. 3); in the caudal two-fifths of the pons the neural structures were relatively well preserved except for descending degeneration of the corticospinal tracts. The superior cerebellar peduncles, supplied by the superior cerebellar arteries, were preserved, as was most of the cerebellum. However, occasional sections of cerebellar cortex disclosed scattered foci of incomplete softening.

The medulla oblongata (Fig. 4) revealed complete descending degeneration of the pyramids in preparations stained for myelin; cellular stains disclosed scattered gitter cells in situ in the pyramids. The hypoglossal nucleus and the nucleus ambiguus appeared essentially normal. The olives showed extensive degenerative change, with demyelination, extremely abnormal ganglion cells (swollen, vacuolated, and sometimes showing central chromatolysis), and considerable hyperplasia of astrocytes with formation of gemistocytic and bizarre glial forms, some binucleated.

Section of the basilar artery through the site of thrombosis revealed complete occlusion of the lumen; the central portion of the thrombus was made up of loose connective tissue, containing scattered hemosiderin-bearing scavenger cells and presenting a few small endothelial-lined channels, in which clumps of red blood cells were seen. The thin medial and adventitial wall of the artery presented atrophic change; the degenerated intima was fused with the organized thrombus. Section through the basilar artery near the caudal extremity of the clot (Fig. 5) revealed a large area of cholesterol deposit in the tremendously thickened intima, opposite which the media and adventitia appeared atrophic. The break-up and disappearance of the intimal elastic layer was well demonstrated. Caudal to the site of thrombosis the basilar artery presented marked intimal hyperplasia. The elastica

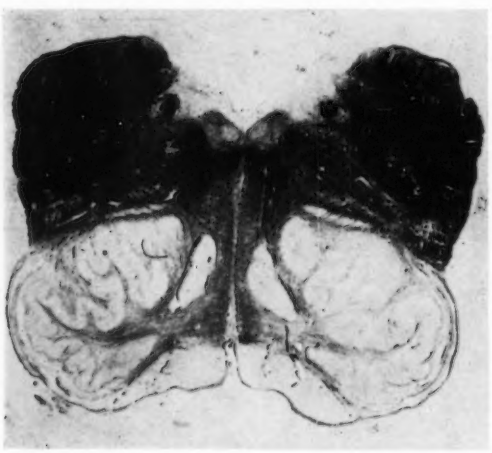

Fig. 4. — Medulla oblongata, showing demyelination of pyramids and pseudohypertrophy of the olives. Weil stain.

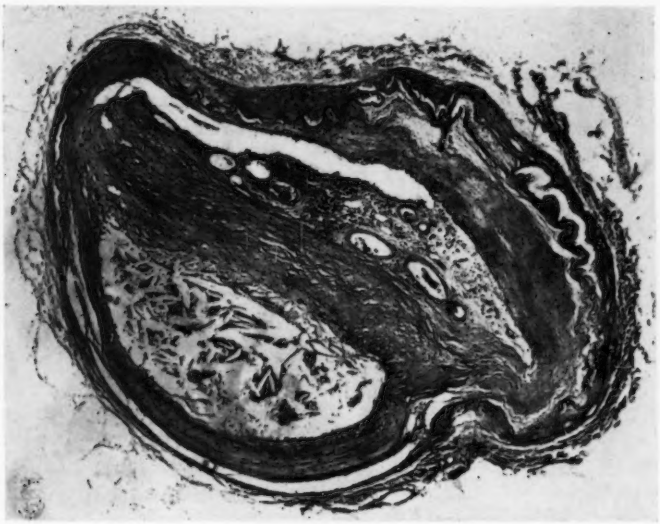

Fig. 5.—Basilar artery just caudal to site of complete occlusion. Weigert's elastic stain.

was frayed and duplicated, and was completely degenerated in a small sector of the vessel. Just above the junction of the two vertebral arteries the basilar artery showed less marked atherosclerotic change.

Comment

Two aspects of this case are worthy of some discussion. The first of these is concerned with the anatomical substratum for the prolonged, irreversible loss of consciousness; the second, with the casual relationship between the accidental high-voltage electrical shock and the subsequent fatal damage to the brain through the intermediacy of basilar-artery thrombosis.

Kubik and Adams,[1] in a study of 18 cases of occlusion of the basilar artery, noted that consciousness was altered from slight confusion to deep coma. Biemond's report[2] of four cases is of particular interest. His third case was concerned with a neurosurgeon's ligating the middle part of the basilar artery with silver clips to control profuse bleeding during operation for acoustic neurinoma. This patient became anarthric and tetraplegic, was able to follow his nurses with his eyes, and had equal pupils; only after an hour did unconsciousness supervene, followed three hours later by death. Biemond's fourth patient lived for a month and remained conscious toward the end, although finally anarthric and tetraparetic; but the occlusion was in the caudal part of the basilar artery.

In our case there was extensive softening in the thalami without actual occlusion of the main trunks of the posterior cerebral vessels, implying that the circulation through these arteries was effected chiefly from the basilar stream, with little help from the carotid circulation.

The experiments of nature supplied by the von Economo type of epidemic encephalitis during and following World War I, in which prolonged disturbance of consciousness occurred and the brunt of the inflammatory attack fell upon the diencephalon and midbrain, called attention to the importance of this part of the brain in the control of wakefulness and sleep. The contributions of a long succession of clinical observers and experimental investigators,[3-12] beginning with Fulton and Bailey in 1929, were in essential unanimity in recognizing the rostral brain stem with its reticular activating substance as essential to the engram system responsible for crude consciousness. However, that the cerebral cortex is the essential substratum of con-

sciousness was emphasized by Bailey,[13] in a recent address, who remarked that it is quite probable that the cerebral cortex may need to be alerted like the tubes of a television set by the reticular formation or other afferent systems before it will transmit, but that "the cerebral cortex alone is capable of that bewildering play of intricate mental process which is characteristic of human mentality."

In our case the reticular formation of the medial tegmentum of the midbrain and upper pons was destroyed by virtue of anemic softening. There was also considerable thalamic destruction, especially on the left side. The cerebral cortex was essentially intact, except for the visual cortex, particularly on the right side, and this latter change may have been a late development.

Terminally, in the course of this patient's illness, palatal nystagmus was discovered. This may be correlated pathologically with degeneration of the central tegmental tract in connection with the destructive softening in the midbrain and upper pons, and with the extraordinarily marked gliosis in the inferior olivary nucleus (pseudohypertrophy).

The electroencephalograms did not show any persistent sleep rhythms and revealed only moderate abnormalities, in contradistinction to the severe clinical picture of persistent abeyance of consciousness.

The second aspect of this case, as to whether electrical injury was in some manner contributory to this patient's death, deserves serious consideration. We were unable to find report of a closely corresponding case in the literature concerned with the effects of electricity on the nervous system. The commonest immediate results of electrical injuries, as seen at autopsy, are small perivascular hemorrhages, particularly in the brain stem.[14-16] Hassin[17] has emphasized that rupture of the elastica of the basilar artery occurs in accidental electrocution.

There are well-documented clinical reports of serious delayed effects of electricity upon the central nervous system, particularly in the German literature. These have taken the form either of delayed bulbar palsy[18] or of spinal atrophic paralysis,[19] but necropsy findings are not given except in the case reported by Karnosh,[20] who found fresh petechial hemorrhages in the medulla, widened perineural spaces, and fibrin formation about arterioles of the cord in the case of a 39-year-old lineman dying six months after an electric shock with clinical signs of bulbar involvement.

Since the advent and widespread use of electroshock therapy, much experimental work on animals has been done to determine whether histopathological changes are produced by the passage of the current. Hassin,[21] in 1949, appraised this work in his textbook, stating that the changes found in electrocution cannot be expected with the weak currents used in treatments for mental disorders and pointed out that the experimental results were on the whole contradictory.

However, reports of death following electroshock treatment of human patients continue to appear in the literature, and where there are cerebral changes, these may have some relevance to the present case of high-voltage electric shock, even though the therapeutic current is of relatively low voltage and intensity. The largest series of fatalities in electroshock therapy was reported recently by Impastato,[22] who collected 254 cases from the literature, including 66 cases of cerebral changes as the cause of death. Among the latter were 16 cases of hemorrhage, thrombosis, or necrosis within the brain. There was only one case of thrombosis of the basilar artery, reported by Eyres.[23] The patient was a 24-year-old woman who had received 24 electroshock treatments during a third course of such therapy. Seventeen hours after the last treatment she was found in status epilepticus and died five hours later. Necropsy revealed thrombosis of the basilar artery, beginning softening of the pons, and petechial hemorrhages in the left "peduncle."

In our case, we cannot ignore the fact that the patient had been well until the electrical injury, and that he developed headache, dizziness, and personality changes shortly after the accident. The sudden collapse more than two weeks after the accidental electric shock obviously was caused by occlusion of the basilar artery. The necropsy findings of arteriosclerotic changes in this artery were so marked that we must assume that arteriosclerosis had existed before the accident, although the extent and severity of such changes at the time cannot be known, since necropsy was performed a full year later. The arteriosclerosis was practically confined to the basilar-artery system.

We assume that the electrical injury damaged the basilar artery and therefore was a factor in the delayed occurrence of thrombosis, by causing hemorrhages into the vessel intima or fragmenting the diseased elastica. The literature tends to support this assumption because of the tendency of high-voltage electrical shock to injure blood vessels.

Summary

A case is described of delayed onset of coma lasting more than a year following high-voltage electrical injury and caused by occlusion of the middle portion of the basilar artery. Extensive encephalomalacia of the midbrain and upper pons, involving the tegmental reticular formation, was found; in addition, thalamic softening (within the posterior cerebral distribution) was present. In view of the clinical course in this case and the known tendency for high-voltage electric shock to injure blood vessels, we cannot exclude a causal relationship, at least as a contributing and precipitating factor, of the electrical injury in the production of the occluding thrombus.

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Responses of Cats to Tactile and Noxious Stimuli

Temporal Summation, Facilitation, Internal Inhibition, and External Inhibition as Examples of Interaction Between Stimuli on a Behavioral Level

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Much of the classical work on spinal reflex activity dealt with the facilitating and inhibiting effects of stimuli upon the responses to subsequent stimuli. Such effects were seen following both the repetition of a single stimulus (temporal summation and reflex fatigue) and the interaction of two different stimuli (facilitation and inhibition).[1] These studies were made easier by two characteristics of the spinal preparation: The parts innervated by the isolated spinal cord were no longer functionally connected with the senses of sight, sound, and smell; and these parts showed very little spontaneous activity, thus permitting any movement that occurred to be causally related to specific stimuli.

On a behavioral level a similar concern for the interaction between stimuli can be found in Pavlov's studies of conditioned reflexes.[2] The terms internal inhibition and external inhibition are closely analogous to reflex fatigue and inhibition. In order to relate quantitatively the magnitude of the response to the effects of specific stimuli, it was necessary to take elaborate precautions to control the distracting sights, sounds, and odors inevitably associated with the procedure and to select a response, salivary secretion, that had a low and predictable level of spontaneous activity. The transition from the alert state to sleep involves a marked decrease in responsiveness to certain stimuli, and many of Pavlov's observations had a direct bearing on the relation of such stimuli to the production of sleep.[2]

There has been a renewal of interest in the effect of stimuli upon the responsiveness to subsequent stimuli and in the general problem of sleep-wakefulness and specific, as well as generalized, alertness, as a result of the recent studies on the reticular formation and related parts of the brain. The first of these experiments dealt with the descending influences of these regions upon spinal reflexes; electrical stimulation of the reticular formation facilitated or inhibited reflex activity.[3] Subsequent use of electrical recording techniques defined its ascending function of maintaining and regulating wakefulness and generalized responsiveness. Lesions of the reticular formation produced a permanent condition of sleep or coma; the animals were both very unresponsive to stimuli, as judged by the lack of motor response, and had an EEG pattern characteristic of sleep.[4] Stimulation of this region, either directly by electrical stimulation[5] or indirectly by peripheral stimuli,[6] caused a change in the EEG in the direction of low-amplitude, high-frequency activity. Since this desynchronization of the EEG was accompanied by behavioral signs of arousal and alertness in the unanesthetized animal,[6] this pattern was considered to represent an activation of cortical function. More recent studies have demonstrated electrophysiologic correlates of facilitation[7] and internal[7,8] and external[8-10] inhibition.

The work on generalized arousal dealt with gross changes in responsiveness to stimuli, such as those accompanying the transition from sleep to wakefulness. Studies

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of the electrophysiologic correlates of conditioning and internal and external inhibition so far have been concerned with the presence or the complete absence of such simple responses as the alerting reaction. However, other experiments have pointed out the role of the reticular formation and related parts of the brain in influencing aspects of behavior (motivation,[11] sexual activity,[12] and rage and fear [13]) that cannot be expressed at this time in simple terms of facilitation and inhibition. A need therefore exists to establish criteria for relating these more complex examples of behavior to the strength of specific stimuli and to the effect of one stimulus upon the responsiveness to others.

As a beginning for such a behavioral study, cats were completely deprived of their senses of sight, sound, and smell. These cats could be placed in the middle of an ordinary room, without restraint, and would remain absolutely unresponsive to the presence and movements of the observer. Their basal activity was sufficiently slight that one could be reasonably certain they would not move for long periods unless purposely stimulated. The observer could walk over to such an animal lying quietly on the floor and be sure that it would neither respond to the approach of the person nor otherwise move until stimulated, and then walk back, sit down, and record the activity of the cat. The recording technique utilized Sherrington's observation [14] that the number of parts of the body involved in a response varied directly with the intensity of the stimulus. Under the conditions of these experiments this was an adequate measure of the magnitude of the response.

Methods

Ten cats were prepared as follows: Under deep anesthesia the aqueous and vitreous humors of the eyes were rendered opaque by an injection of absolute alcohol, which precipitated the proteins. This procedure also caused acute glaucoma and degeneration of fibers in the optic nerve. The cats did not respond to light. The cochlea was destroyed bilaterally with a dental burr, without producing signs of vestibular dysfunction. To gain access to the olfactory bulbs, the frontal sinus was widely opened and the exposure extended by removing the medial walls of the orbits. The olfactory bulbs were then removed by suction under direct visualization. These blind, deaf, anosmic preparations will henceforth be referred to as BDA cats.

The cats were free to move about in a 4×4 ft. pen during the experiments. Their activity was recorded from the time they were placed in the pen until they were removed. In order to facilitate the recording of activity, a rubber stamp bearing a simplified diagram of a cat was designed. Record sheets were made with one impression of the stamp for each recording interval (Figs. 1 and 2). Those parts of the animal's body that moved at a particular time were indicated by darkening with a pencil the appropriate part on the corresponding diagram. Additional notations were made whenever the cat's activity included a specific component of interest that could not be adequately recorded on the diagrams. The convention was adopted of filling in the trunk segment of the diagram to indicate walking instead of flexion of the trunk.

The recording interval was usually 15 seconds, except when sudden changes in activity were expected; then it was shortened to 5 seconds. However, in preparing the accompanying illustrations, limitations of space made it necessary to consolidate the recorded movements occurring in four consecutive 15-second intervals and represent them on a single figure.

Three different noxious stimuli were used from time to time: (*a*) an electric shock of one-half second's duration delivered via a metal grid covering the floor, (*b*) a single sharp blow to the face with a plastic fly swatter, and (*c*) a brief pinching of the tip of the tail. Various tactile stimuli were used, e. g., firm petting, lightly running the fingers once up the middle of the cat's back for a distance of about 4 in. (touching only the fur), and lightly touching only a few hairs on the cat's back.

Results

General Characteristics of the Experimental Animals.—After a recuperative period of 10 to 14 days, the cats ate well, cleaned themselves, and appeared well adjusted to life with sensory impairment. Several have been kept more than six years. As long as they continued to be handled, they remained friendly and affectionate. Their tendency to sleep was increased by the operation. When hourly checks were made on BDA and normal cats in their

cages in the animal quarters from 9 a. m. to 5 p. m., the BDA cats were found lying down and apparently asleep 99 times out of 100 consecutive observations; the normal cats were lying down only 12 times, and appeared asleep on only 5 of these occasions. When removed from their cages and placed in a free environment, they showed the same kind of investigational activity as an intact cat, but for a shorter time. They were absolutely unresponsive to visual, auditory, and olfactory stimuli. The experimenter was able to move about freely without affecting their behavior in any way. Except for their tendency to sleep more of the time and their unresponsiveness to visual, auditory, and olfactory stimuli, the BDA cats exhibited typical feline behavior.

Basal Activity and Response to the Experimental Environment.—The activity of these cats when not purposely stimulated represents the background against which the responses to specific stimuli must be evaluated. It is therefore essential to consider the character and frequency of such movement in detail. The BDA cats showed so little activity in their cages that it was easy to record every movement a cat made during a day.

The most frequent activity was shifting position. Most frequently this consisted of changing the position of one or two extremities, or shifting the position of the head on the paws. Occasionally the cat would get up, turn all the way around, and assume an entirely different position. Even when a period of more varied activity occurred, it often began with the cat's stretching, which itself suggested that the cat was responding, in part, to the cumulative effects of having maintained some position too long for complete comfort. It therefore seems reasonable to assume that these shifts in body position were the result, at least in part, of various stimuli, which increased in intensity with continued maintenance of one position until the cat moved; the movement, by changing the position, temporarily decreased the intensity of these particular stimuli.

The next most frequent activity was licking. Occasionally the cat would suddenly sit up and start to lick vigorously or bite a particular spot on its body. At such times it appeared to be responding to some specific cutaneous stimulus, such as a flea or sudden itch. More frequently, the licking was less intense and more varied. Even in these instances, however, there was a fine degree of coordination involved, and the object of the licking did not appear to be determined by chance; it would lift its leg and turn its head at the same time. It also seemed that the cat was responding to some cutaneous stimulus, however slight it may have been, for it would often pause for a moment and then return to licking the same spot, perhaps more vigorously the second time, as though it had not accomplished its purpose and relieved the sensation. It seemed, therefore, that licking was most frequently a response to some cutaneous stimulus, such as an itch, or dryness, or stickiness, and that the licking somehow relieved or modified the sensation so that the response ceased.

Very occasionally the cat would get up and walk around fairly continuously for two or three minutes. This activity had the appearance of exploratory or seeking behavior, and was especially characterized by frequent pawing of the sawdust and a tendency to turn around backward, rather than in the usual forward progressing circles. Such activity almost always led to urination or defecation.

The cats were responsive to the gross vibration produced by opening the cage door, and this apparently had become associated with feeding. When they were hungry, this stimulus would cause them to get up and walk about until they found the food. Unless they had been fasted for several days they would never eat very long at a time; rather, they would get up and eat a few mouthfuls several times during the day. Fasting increased their activity, but did not change its character. The increase was manifested by more frequent shifts in position, more frequent licking, and occasional brief periods of exploratory activity. The

general level of activity was also increased on days when the temperature of the room was noticeably lowered.

The foregoing description adequately presents the range of activity of the cats in their cages, except for twitching an ear when a fly would alight on it, or occasionally scratching themselves. In general, their activity duplicated that of a normal cat under similar circumstances, except for its frequency and intensity. They never showed the restless pacing back and forth that normal cats often show near feeding time, for example. The frequency of the minor shifts in position was about once every 10 minutes; the intervals between licking averaged about an hour, and movement that could be called walking, even though it consisted of only two or three steps, occurred an average of every 2 hours under the usual conditions. Several days of observing for six hours a day might pass without seeing the cat take as many as 20 consecutive steps.

If it is correct to assume that these activities represented responses to minor, but specific, stimuli, then one of the effects of conditions, such as hunger and cold, was to increase the responsiveness to these stimuli; certainly, hunger and cold were accompanied by an increased frequency of responses taken from this limited repertory. It was similarly apparent that once a response of considerable magnitude occurred, whatever its cause, the responsiveness to these other stimuli was increased. When walking occurred, it seldom ceased abruptly; it tended to be followed, instead, by a series of responses involving movement of a progressively decreasing number of parts of the body. Thus the cat would usually lick itself before lying down and then would appear to have some difficulty in finding a comfortable position; i. e., there was a gradually decreasing frequency of shifting position as the cat became more deeply asleep.

Most observations on the responses to specific stimuli were made with the cat in the experimental pen. This required that the door of the cage be opened and the cat picked up, carried to the next room, and placed on the cement floor of the pen. The complex group of stimuli associated with this procedure exerted an effect on the subsequent activity. For the first few minutes after being placed in the pen the cat walked about almost continuously, apparently investigating its surroundings. It frequently paused to lick itself. The walking gradually became less continuous, and the licking became less frequent. Shifts in position were frequent when it first lay down, and decreased with time. When all activity had sufficiently decreased, the cat appeared deeply asleep. The duration of sleep varied, but was usually over an hour. Then the cat often arose, stretched, licked itself a few times, walked a few turns around the enclosure, and then returned to sleep. When more prolonged periods of spontaneous activity were observed, they usually were associated with a developing need for urination or defecation. Figure 1 is an abridged record of the movements of a cat for the first 42 minutes after being put in the pen.

Response to Tactile Stimuli.—The responsiveness of the cats varied with the length of time they had been in the pen and the length of time they had been quiet. For this reason it was customary to stimulate a cat only after it had been quiet for five minutes. This usually occurred when it had been in the pen 20 to 30 minutes. Under these standardized conditions of testing, the responses to tactile stimuli were remarkably predictable. Running a finger once lightly up the cat's back would cause it quickly to sit or stand up and turn its head as if to "look" about. Following this *alerting response* the cat would remain immobile for one or two seconds. Then it might lick itself, perhaps stretch, or walk around a little. The activity initiated in this way never ceased abruptly, but tended to be followed by a series of responses of decreasing frequency and involving movement of progressively fewer parts of the body. The cat was usually quiet again within one or two minutes. The responses of any one cat were

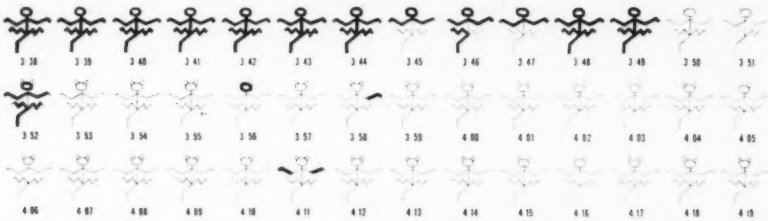

Fig. 1.—A record of the movements of a cat for the first 42 minutes after being put into the experimental pen. It is presented to illustrate the method of recording. It represents the background, or basal, activity against which the responses to specific stimuli must be evaluated. The recording intervals are one minute in duration. Thus, the diagram labeled 3:38 represents all the movement occurring between 3:38 and 3:39. From 3:38 until 3:45 the cat walked about fairly continuously, apparently investigating its environment. In addition to the motor activity recorded on the diagram, other notes were made, as follows: Between 3:42 and 3:43 she sat down and licked both forelegs. In doing this she lifted her left forepaw off the floor, but not her right. She then resumed walking around. At 3:44:20 she lay down. Twenty seconds later she shifted her position slightly. At 3:45:40 she shifted the position of her head and both forelegs. In doing this she tucked her left forepaw under. Between 3:46 and 3:47 she licked both forelegs, her left hindleg, and tail. The left forepaw was not removed from the floor. She then lay down, shifted her position slightly, and was quiet until 3:47:15, when she again shifted the position of her head and forelegs, tucking both forepaws under. At 3:48:50 she got up, walked once around the pen, and lay down. This took 20 seconds. At 3:49:40 she shifted her position slightly. She was not seen to move again until 3:52:10, when she sat up, licked herself for 35 seconds, and lay down. Between 3:56 and 3:57 she shifted the position of her head on her paws. Between 3:58 and 3:59 she tucked her right forepaw under. Between 4:11 and 4:12 she shifted the position of both forelegs.

almost identical from one day to the next, even when tested over a period of years.

The nature of the alerting reaction was more apparent when the cat was touched while some other activity was already present. There was, for example, a complete cessation of activity when the cat was touched while walking about; however, after one or two seconds the activity would continue as before. When the cat was touched while licking itself, the alerting response temporarily inhibited the licking, but following this the cat would usually get up and walk around. If it is assumed that all activity, even though apparently spontaneous in nature, is actually a response to stimuli, this cessation of movement must represent a temporary decrease in responsiveness to, or a deflection of attention from, these stimuli. Such a decreased responsiveness has been termed *external inhibition*.[2]

The concentration of activity that followed tactile stimuli stood out sharply against the background of very little movement. However, there is reason to believe that much of this movement represented a temporary *facilitation* of responsiveness to other stimuli, rather than a response specific to the tactile stimulus. Except for the initial alerting response, all the activity that comprised the after-response to the tactile stimulus (walking, licking, shifting position) was also characteristic of the responses to other stimuli (hunger, cutaneous, positional) that were present to varying degrees all the time. One of the effects of the tactile stimulus therefore appeared to be to increase the frequency or facilitate the occurrence of these normally occurring responses. The walking that sometimes occurred was indistinguishable from the seeking behavior of a hungry cat or the exploratory activity that followed placing a cat in the pen, and more frequently followed tactile stimuli when the cat was hungry or had only recently been placed in the pen. Similarly, there was nothing characteristic of the licking or shifts in position to distinguish them from the same activities occurring under apparently spontaneous conditions.

Various tactile stimuli were used from time to time, and these may be arranged in the order of their apparent strengths: (1) lightly touching only a few hairs on the

cat's back; (2) lightly running the fingers once up the middle of the cat's back for a distance of about 4 in. (touching only the fur); (3) passing the hand firmly from head to tail, and (4) continuous petting. The magnitude of the response, as measured by the number of parts of the body that moved, varied directly with the strength of the tactile stimulus, to the extent that the stimulus itself could be quantitated. Not only could the magnitude of the initial specific response be correlated with the strength of the stimulus, but the magnitude of the nonspecific after-response as well. After a very weak tactile stimulus, the cat would usually turn its head, then shift its position slightly, and return to sleep. With a somewhat stronger stimulus the cat would often sit up and "look" around, then lick itself, assume a more comfortable position, and return to sleep. If the stimulus was strong enough, the cat would always stand up and walk around.

In addition to their effect upon the responsiveness to other stimuli, tactile stimuli exerted both a facilitating and an inhibiting effect upon the responsiveness to subsequent applications of the tactile stimulus itself. When a weak tactile stimulus was repeated at intervals of one minute, the movement following the second and third applications was often greater than the initial response. This *temporal summation* was occasionally produced when the intervals were two minutes, but not when they were five. When the weak tactile stimulus was applied at five-minute intervals, the responsiveness to the tactile stimulus progressively decreased (*internal inhibition*). There was a decrease both in the number of parts of the body that moved and in the duration of activity that followed the tactile stimulus. As a rule, the cat failed to respond at all to the stimulus after 6 to 10 repetitions and appeared to be asleep. This degree of internal inhibition was not permanent; if repetition of the stimulus was continued long enough, responses would recur. These periods of renewed responsiveness corresponded in frequency to the periods of spontaneous wakefulness of these cats and therefore were probably due to the facilitating effect of other stimuli (hunger, cutaneous, positional) when these increased in strength. If other stimuli were interposed, or if the tactile stimulus were repeated at too rapid a rate, e. g., continuous petting, extinction of the response would not occur.

Response to Noxious Stimuli.—The response to a strong noxious stimulus differed in two important respects from the response to the tactile stimuli so far considered: The magnitude of the initial response, as judged by the number of parts of the body involved, was much greater, and the initial response was followed by a period of greatly decreased, rather than increased, activity. Not only was there always vigorous movement of the entire body, but vocalization and some evidence of visceral response occurred as well. There was an immediate motor response that included some or all of such signs of attack and withdrawal as hissing, striking at the stimulus, withdrawal to a corner of the pen, crouching, retraction of the ears, and piloerection. This phase was short-lived, lasting only a few seconds, and was followed by a phase of quiescence, almost entirely devoid of movement. In the experiment illustrated in Figure 2, a cat was placed in the pen and immediately hit in the face with a plastic fly swatter. Without this noxious stimulus the cat would have been expected to show the same amount of activity as it did in Figure 1. The marked (external) inhibition of this activity can be seen by comparing the two figures. During the early part of the quiescent period the cat did not appear relaxed. It sat in a crouched, withdrawn attitude, with ears laid back, as though awaiting a repetition of the noxious stimulus. Not only was it unresponsive to whatever stimuli produced the prolonged activity in Figure 1, but it was relatively unresponsive to tactile stimuli also, little if any movement resulting. This tonic immobility always changed into a state of apparent sleep without any sharp transition.

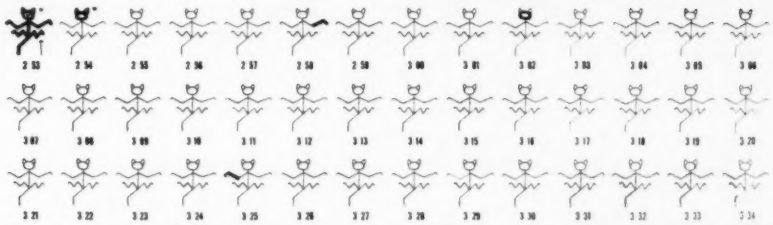

Fig. 2.—The record of the movement of a cat following a strong noxious stimulus. One week following the experiment shown in Figure 1, the same cat was again placed in the experimental pen. She was immediately given an electric shock via a metal grill covering the floor. This stimulus produced an immediate motor response that included movement of almost every part of the body, as well as vocalization and piloerection. This part of the response was of short duration. The cat retreated to a corner of the pen and lay down. The time between the noxious stimulus and the cat's lying down was 12 seconds. Following this there was a long period with very little movement. This represents a marked (external) inhibition of the normal activity which usually followed placing the cat in the pen, and which is shown in Figure 1. The cat at first appeared to be in a state of watchful expectancy, even though she was lying down and not moving. This gradually passed into a period of apparent sleep, without any intervening period of activity.

When a weak noxious stimulus was used, both the magnitude of the response and the amount of external inhibition were less, and external inhibition was eventually replaced by facilitation of responsiveness to other stimuli. Both of these factors were responsible for the fact that the response to a weak enough electric current or pinch could not be distinguished from the response to a tactile stimulus. 1. The fact that the response to a strong noxious stimulus always included vigorous movement of almost every part of the body, as well as vocalization and piloerection, clearly set it apart from the alerting response to a tactile stimulus. When the magnitude of the response was less, it no longer gave the impression of fear or rage. 2. The prolonged immobility or external inhibition that followed a strong noxious stimulus completely prevented the after-response usually associated with a tactile stimulus. When the strength of the stimulus was less, external inhibition became very slight and was followed by facilitation of responsiveness to other stimuli; this facilitation was often manifested by exploratory or seeking behavior.

Behavioral Changes Associated with Increased Responsiveness to Tactile Stimuli.

Five of these cats were not petted or handled at all for periods varying from one to two years. This resulted in a marked change in the nature of their responses to tactile stimuli. They were fed each day, and their cages were cleaned approximately once a week. The latter procedure was the same for these as it was for all the other cats. It involved pulling the tray out slowly enough that the cat could easily step out onto the underfloor of the cage. After cleaning, the tray was gently reinserted, and the cat would step back in without undue excitement. Thus these cats were treated in a manner identical with that of all other cats during this period except that they were never picked up or petted. However, as a result of these prolonged periods of isolation from tactile stimuli, their responsiveness to such stimuli increased greatly and exhibited all the characteristics of attack, withdrawal, and prolonged subsequent inhibition of movement ordinarily seen only in response to strong noxious stimuli. Subsequent repetition of the tactile stimulus decreased the responsiveness of the cats to these stimuli. However, while they could be made completely unresponsive to the tactile stimulus within a matter of minutes, very continuous repetition of the stimulus over a period of weeks was necessary to reproduce the normal friendly response to petting.

When gloves were worn and petting was continued despite the cat's attack, acute

extinction of the response occurred. However, there was no phase during the process when the normal response to petting was seen; there was no phase of friendly seeking behavior. Attack alternated with withdrawal and hissing. Attack and withdrawal gradually became less frequent and were replaced by increasing periods of immobility. After a few minutes the cat could be petted without fear of attack, because it was completely unresponsive to the stimulus and apparently deeply asleep.

Continued repetition of the stimulus, however, eventually restored the normal character of the response. These sessions of acute extinction were repeated many times a day. Sometimes a cat was petted continuously for an hour at a time. Gradually the cumulative effects of this chronic repetition began to appear. Both the magnitude of the initial response and the amount of external inhibition associated with it decreased. Throughout this period of many days or weeks, everything that facilitated the cat's responsiveness to the tactile stimulus caused it to respond again with attack or withdrawal. The cat might accept petting while lying down and not excited; however, when walking about, whether the walking was due to some known external or unknown internal stimulus, the cat would again respond with attack, withdrawal, and subsequent inhibition of movement. Sometimes the cat would respond to the first stimulus in a friendly manner, stretch, and stand up, only to respond to repetition of the stimulus with attack and withdrawal, as though its responsiveness had been facilitated by the movement itself. The outbursts of avoidance behavior during the later stages of training tended to be followed by less and less evidence of external inhibition. After the petting had been continued for many hours a day for three to seven weeks, the cats all responded once again in a normal, friendly, feline fashion even when walking about. This lasting change was entirely the result of repetition of the tactile stimulus and was not encouraged in any way by rewards such as food.

Comment

The observations reported here are directly related to two important aspects of behavior, sleep versus wakefulness, and seeking versus avoidance activity. It has long been apparent that peripheral stimuli are important in maintenance of the alert state. Decreasing movement and decreasing various internal and external stimuli are certainly conducive to sleep. However, since peripheral stimuli are never decreased to zero, the responsiveness to the stimuli that are present must also be important. Sleep is a state of decreased responsiveness to stimuli. There are at least three means of producing a decreased responsiveness: (1) by removing certain stimuli and thereby eliminating their facilitating effect upon the responsiveness to other stimuli; (2) by internal inhibition, and (3) by external inhibition. However, since external inhibition is associated with the focusing of attention on some specific stimulus and thus involves an increased, as well as decreased, responsiveness, studies concerned with the production of sleep have centered on the role of internal more than on external inhibition. Outside the laboratory sleep is seldom artificially imposed by restricting the animal's movement, by decreasing the number of stimuli, or by monotonous repetition of a stimulus. Instead, the animal may at times seek out a spot where these conditions prevail, and may assume a comfortable position and close its eyes, giving the impression of purposeful behavior. Any comprehensive theory of sleep should therefore also attempt to define the factors that determine the occurrence of this apparently spontaneous activity.

The role of the facilitating effect of stimuli in maintaining the alert state has been shown by recent experiments on the reticular formation. Neurons in the reticular formation are activated by collaterals from the direct sensory pathways. If this background of facilitation is blocked either by anesthesia [15] or by destruction of the reticular formation,[4] the animals remain

asleep and unresponsive, even though the direct sensory pathways continue to conduct impulses. Complementary studies on the effects of peripheral deafferentation have not been reported. It is, therefore, of interest to note the extent to which depriving these cats of their senses of sight, sound, and smell increased their tendency to sleep.

When they were not purposely stimulated, the responsiveness of these cats often passively sank to very low levels, and they appeared to be deeply asleep. At such times the single application of a fairly strong tactile stimulus would not awaken the animal. However, sufficient repetition of the stimulus (petting) always caused the cat to get up and walk around, thus demonstrating the importance of the facilitating effect of one stimulus upon the responsiveness to subsequent ones.

The neurons of the reticular formation are especially susceptible to the inhibition that accompanies repetition of a stimulus and, when inhibited, fail to exert their facilitating effect on the cerebral cortex. Repetition of a stimulus leads to a progressive loss of the desynchronization effect of the stimulus upon the EEG and the development of a pattern corresponding to sleep.[7] Thus, there can be little doubt that proper repetition of a stimulus leads not only to a decreased responsiveness to the stimulus that is being repeated but to a decreased responsiveness to other stimuli as well. However, there is disagreement regarding the cause of this more generalized lack of responsiveness. Pavlov said that sleep and internal inhibition were "one and the same process."[2] By this he meant that there was an active irradiation of the inhibitory process from the original stimulus to involve, eventually, almost all stimuli. When familiar weak tactile stimuli were repeated at five-minute intervals in the present experiments, the BDA cats became, temporarily, completely unresponsive to the tactile stimulus. The cats became relatively unresponsive to other stimuli also, and appeared asleep. However, there was no evidence that they became less responsive to these other stimuli than they would have over a similar period if not stimulated. Since repetition of the tactile stimulus decreased the responsiveness to a stimulus that would not otherwise have been present, it was concluded that internal inhibition permitted, rather than produced, sleep, i. e., that it permitted sleep to occur despite the continued application of the tactile stimulus, and that the decreased responsiveness to other stimuli was due to the decrease in the facilitating effect of the tactile stimulus as the cat became less responsive to it. This is consistent with recent EEG findings.[7]

Pavlov's dogs were restrained in a harness and trained to remain quiet. Many of the experiments of others involving electrical recording are performed in curarized animals. Any such restriction of movement is favorable for the development of both internal inhibition and sleep. However, in the present experiments movement was not restricted by artificial means, and the presence of movement both facilitated the responsiveness of the animal to stimuli and interfered to some extent with the process of internal inhibition. When these animals were accustomed to being handled, continued firm petting persisted in producing prancing and rubbing for long periods of time and was not accompanied by any obvious decrease in responsiveness or the production of sleep. External inhibition, which has largely been overlooked as a factor in the production of sleep, played a more important role in these experiments because of its ability to cause a cessation of movement. When a cat was placed in the pen, sleep occurred more quickly after a strong noxious stimulus than when the cat was not so stimulated. When an unusual degree of external inhibition was associated with the tactile stimulus, as was the case following prolonged isolation from such stimuli, continued petting caused the cat to become completely unresponsive to the tactile stimulus (internal inhibition) and relatively unresponsive to all other stimuli (external inhibition). It was under these conditions that sleep was rapidly and actively

produced. This was the only situation in which the responsiveness to tactile stimuli was decreased below the level that could occur spontaneously; it was the only situation in which petting would not awaken the cat. It was then often necessary to shake the cat or pick it up in order to awaken it.

It has also been apparent for a long time that peripheral stimuli are important determinants of seeking and avoidance activity. The drive-reduction hypothesis [16] states that strong external or internal stimulation excites the animal to activity. When this activity reduces the level of stimulation, either by permitting escape from a noxious stimulus or by satisfying some instinctual need, the lowering of excitation is interpreted as a reward, and the responses leading to it are reinforced. Stimuli that serve as cues for this reduction of tension become actively sought, while stimuli that signal an increase in tension are actively avoided.

Recently, however, it has been shown that electrical stimulation of the rhinencephalon and brain stem has rewarding and punishing effects and can motivate seeking and avoidance behavior.[11] Many of these are the same areas that, when stimulated, exert facilitating and inhibiting effects on the responsiveness of the animal to peripheral stimuli. If friendly seeking and unfriendly avoidance are interpreted to represent opposite extremes on the behavioral scale, instead of reflecting differences in the responsiveness of the animal, many of the ablation studies involving these regions appear to contradict each other. For this reason, it is interesting to speculate that, if stimulation of a part of the brain serves to satisfy some instinctual need, destruction of the same region might lead to a chronic state of unsatisfied need. This latter condition could be manifested either by an increase in seeking behavior or, if the lack of satisfaction was greater, by a tendency to exhibit rage or fear. For example, lesions of certain parts of the rhinencephalon produce an increase in friendly seeking behavior manifested by hyperactivity, increased following, increased sexual activity, and an elevated rage threshold.[12,17,18] Lesions of closely related parts of the rhinencephalon produce unfriendly avoidance behavior, evidenced by hypoactivity, withdrawal rather than following, apparently decreased sexual activity, and rage in response to petting and other innocuous stimuli.[13,18-20] These differences appear earliest and are most marked in response to tactile stimuli, particularly when these have a sexual significance.[17,18,20] Sometimes these apparently opposite types of behavior have been reported to follow identical lesions.[12,13,18] However, some of these contradictions can be resolved if it is assumed that one effect that all these lesions have in common is to make the animals abnormally responsive to tactile stimuli—in some cases to the point of unusually persistent seeking behavior, in other cases to the further point of unfriendly avoidance behavior.

It is surprising that stimulus-response theories of behavior have not incorporated, to a greater extent than they have, the concept that variations in responsiveness influence the behavioral characteristics of the animal's response. A unique opportunity in this direction was offered in the present experiments by having an animal that would respond to the same tactile stimulus at one time by continued sleep or relative indifference, at another time by friendly and vigorous seeking behavior, and at still another time by very unfriendly avoidance behavior. Since the strength of the stimulus was not changed, these different types of behavior must have reflected differences in the responsiveness of the cat. The behavioral nature of the response was predictable and could be manipulated throughout the entire range simply by varying the frequency of repetition of the stimulus.

In these experiments tactile stimuli were normally followed by a facilitation of responsiveness to other stimuli; and this facilitation, if sufficiently great, resulted in exploratory or seeking behavior. If the tactile stimulus were weak or its effect had been decreased by repetition, facilitation was slight and was manifested by shifting posi-

tion and licking. When the stimulus was stronger, facilitation produced exploratory activity. There was nothing specific about this activity that would permit one to decide what it was the cat was seeking. However, if the stimulus was petting, the response gave every evidence of being pleasurable. Petting itself was accompanied by purring and also by treading and rubbing against the hand, movements that did not tend to remove the cat from the source of stimulation. Cessation of petting was followed by vigorous exploratory activity, as though the cat were looking for the stimulus. It may well be that the mesencephalic reticular formation mediates this facilitating effect of one stimulus upon the responsiveness to other stimuli. In this regard it is interesting to compare the initial alerting and subsequent nonspecific after-response in these cats to the "phasic" and "tonic" EEG arousal reactions, as defined by Sharpless and Jasper.[7] The phasic reaction is immediate, lasts only a few seconds, and is dependent on the direct sensory pathways to the thalamus; the tonic reaction has a latency up to 30 seconds, may last for several minutes, and is dependent on the activity of the mesencephalic reticular formation. Extinction of the phasic reaction is specific for the stimulus repeated, whereas extinction of the tonic reaction is relatively nonspecific. Dell has referred to stimulation of the reticular formation producing exploratory activity.[21]

Whether or not it is accepted that facilitation produced the seeking behavior, or even that it was the tactile stimulus that was being sought, the ability of petting to produce exploratory activity was directly related to the responsiveness of the animal to the tactile stimulus. Just as repetition may decrease the responsiveness to a stimulus, in these experiments extreme lack of repetition made the animal abnormally responsive. After this had occurred, the cat responded to petting with every evidence of rage and fear. As might be expected, repetition of the stimulus decreased the animal's responsiveness once again. However, it did so more quickly and more completely than when the cat had been accustomed to being petted. It also caused the animal to become completely unresponsive and deeply asleep without passing through any phase of exploratory activity. This was because the unusual amount of external inhibition associated with the stimulus caused the animal to become relatively immobile. The dependence of the behavioral nature of the response upon the responsiveness of the animal is further shown by the fact that after several days of repetition the cat would accept petting while lying down and not excited; but when touched while walking about, it would again respond with attack, withdrawal, and subsequent inhibition of movement. The normal friendly response to petting reappeared only after repetition over a period of weeks. After the responsiveness of the animal was decreased in this manner, the unusual degree of inhibition of movement was no longer associated with the tactile stimulus, and exploratory activity once again appeared.

Thus there were times when the cats actually seemed to seek sleep, and there were other times when they seemed to seek stimuli which, for a time served to keep them awake. These differences were due to the stimuli present at any time and the responsiveness of the cat to these stimuli. Lowered responsiveness or weak stimuli were not conducive to sufficient waking for stimulus seeking; the cat merely tried to become more comfortable and went back to sleep. Very heightened responsiveness or strong (noxious) stimuli produced external inhibition which led to immobility or the active avoidance of stimuli and the subsequent occurrence of sleep. It was only with the proper intermediate degree of responsiveness and the proper combination of stimuli that exploratory activity or stimulus seeking was produced.

Summary

Ten blind, deaf, anosmic cats were studied as long as six years. They spent a much greater percentage of their time asleep than

did normal cats. Their spontaneous activity was so low that it was possible to record every movement they made during a day. Most of the activity that did occur when they were not purposely stimulated could be ascribed to stimuli that were always present to varying degrees. The responses to tactile stimuli were very predictable as long as variables such as frequency of stimulation (temporal summation and internal inhibition), strength of stimuli, and other factors that would change the animals' responsiveness (length of time in the pen, hunger, etc.) were controlled. Although the concentration of activity that followed tactile stimuli stood out sharply against the background of very little spontaneous movement, there was evidence that much of this activity represented a temporary facilitation of responsiveness to other normally present stimuli, rather than a response specific to the tactile stimulus. The response to a strong noxious stimulus differed in two important respects from the normal response to tactile stimuli: The magnitude of the initial response, as judged by the number of parts of the body involved, was much greater, and the initial response was followed by a period of greatly decreased, rather than increased, activity (external inhibition). When a cat was placed in the pen, sleep occurred more quickly after a strong noxious stimulus than when the cat was not so stimulated. If they were handled regularly, they remained friendly and affectionate, as before the operation. Except for their tendency to sleep more of the time, and their lack of response to visual, auditory, and olfactory stimuli, they exhibited typical feline behavior. However, isolation from certain tactile stimuli for periods of one to two years caused them to react to the recurrence of these stimuli by attack, withdrawal, and a prolonged subsequent inhibition of movement, identical with that which followed a strong noxious stimulus. When petting was continued despite the cats' attack, they became completely unresponsive within a few minutes, although external inhibition played a more important role in this change than internal inhibition. The animals' normal, friendly, seeking behavior in response to petting was restored only after petting for many hours a day for several weeks; this lasting change was the result of internal inhibition. The factors influencing the occurrence of sleep in these cats were also analyzed.

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Prognosis in Convulsive Disorders

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Introduction

This article is concerned with the prognosis and response to treatment in convulsive disorders. Seizures were classified according to electroencephalographic criteria, to evaluate whether initial electroencephalographic data would be helpful in determining the prognosis. The prognostic implications of various clinical data are considered.

Selection of Patients

It is the policy of the Department of Neurology of the Bowman Gray School of Medicine that each patient with a convulsive disorder have an electroencephalographic examination as part of the initial evaluation. Return visits are scheduled at short intervals, and treatment is intensive. Medications are changed if control of seizures is not achieved, so that uncontrolled patients receive a number of drugs. Electroencephalograms are obtained repeatedly to assess the response to treatment. Representative sections of each electroencephalogram are saved; the findings are classified, and the classification is recorded on a punch card.

Selection of patients for the present study was based on the following criteria:

1. The patient was observed for a period of at least two years.

2. At least two of the electroencephalograms obtained on the patient showed definite abnormalities.

3. Patients whose seizures were caused by brain tumor, angioma, cerebrovascular disease, presenile or senile degenerative disease, or acquired neurosyphilis were excluded.

A total of 228 patients fulfilled these three criteria. The period of observation on these patients ranged from 2 to 15 years, with an average of 4.7 years per patient. The number of electroencephalograms obtained on these patients ranged from 2 to 11, with an average of 3.3 per patient.

This sample may not be representative of the total epileptic population, owing to the criteria for selection. It seems impossible, however, to obtain a completely unselected group of patients with convulsive disorders in a neurologic center, because referral of patients in itself leads to selection. The fact that patients with consistently normal electroencephalograms have been excluded is a definite objection to our material. It may well be, however, that this number is small, since repeated electroencephalographic examinations were performed and activation methods (prolonged sleep records, photic stimulation, pentylenetetrazol [Metrazol]) were frequently used in doubtful cases. However, the method of selection probably resulted in a preponderance of patients who were difficult to control.

A second objection is that the number of patients in certain categories was small, so that it was difficult to draw statistically valid conclusions in these subgroups.

Review of Literature

Most recent studies on the response to treatment in convulsive disorders consider the response to a single new medication during a short follow-up time. In investigations of the long-term prognosis in convulsive disorders the number of completely controlled patients ranges from 26% to 75%.[1-7] This discrepancy is probably caused by differences in the type of patients and the type of seizures in the various studies. Some authors mention that seizures in patients with mental retardation and definite organic seizure etiology are more difficult to control,[1,2,5,8] though not all agree.[3,7] As far as seizure types are concerned, patients with only grand mal seizures do better than patients with minor and/or focal seizures, though it is pointed out that in the group of patients with focal seizures, those with focal motor or sensory seizures have a relatively good prognosis, in contrast to those with

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psychomotor seizures due to a temporal lobe focus.[3,7,9] Study of the literature reveals quite clearly that many additional data are necessary before the probable prognosis in an individual patient with seizures can be evaluated. One of the major difficulties in comparing data from different authors is the difficulty inherent in classification of seizures.

Seizure Classification

In trying to classify seizures, one time and again is struck by the tremendous variability and individual differences in convulsive disorders. Certain entities, such as classical petit mal or psychomotor seizures with a corroborative anterior temporal lobe spike focus in the electroencephalogram, stand out, but in many instances one has to weigh carefully many factors before a patient can be assigned to a diagnostic category.

To label a seizure according to its clinical manifestations meets with almost insurmountable difficulties. Many auras are quite unspecific, and it is often extremely difficult to obtain an accurate description of the seizure pattern. There were several patients in the present series with focal spike activity in the electroencephalogram who had only grand mal seizures while asleep.

A combined clinical and electroencephalographic approach, as is most commonly used, may easily lead to prejudicial interpretations in a study concerned with prognosis. A purely electroencephalographic classification has the advantage of being most objective, particularly when the final classification depends on at least two abnormal electroencephalographic tracings in each patient. It was therefore decided to use a purely electroencephalographic system of classification. The criteria for classification are those of Jasper,[10] with minor modifications. The selected categories are indicated in the first column of Table 3.

1. *Focal Group.*—In this group are included those patients in whom any form of paroxysmal discharge in the electroencephalogram consistently and repeatedly originated from a local area of one hemisphere. The abnormal discharge might be limited to this one cerebral region or, in case of bilateral paroxysmal abnormalities, would show a clear-cut focal preponderance and persistent focal phase reversal. This category has been subdivided into anterior temporal, posterior temporal, frontal, occipital, and centroparietal. (Central and parietal were grouped together because of the great similarity in seizure patterns and other data.) In a few instances the abnormality was unilateral, did not involve the whole hemisphere, but could not be definitely localized in one particular area. This was mainly caused by the infrequent occurrence of the abnormal discharge. These cases were classified as having a "unilateral poorly localized focus."

2. *Hemispheral Group.*—The paroxysmal discharges originated from one hemisphere in this group; but the greater portion of the hemisphere showed abnormal electrical activity, and paroxysmal activity from multiple foci within this area shifted in maximum voltage from time to time.

3. *Group with Bilateral Synchrony.*—The paroxysmal discharges occurred in the same form and with equal voltage synchronously from homologous areas of the two hemispheres. The paroxysmal discharges might consist of 3-per-second spike-and-wave activity (16 patients), slow spike-and-wave complexes or "petit mal variant" (6 patients), multiple spike-and-wave complexes (11 patients), or bursts of rhythmic slow-wave activity (8 patients).

4. *Group with Diffuse Dysrhythmias.*—The electroencephalogram showed all of the following abnormalities: (*a*) The electrical activity was almost continuously abnormal and showed mixed irregular forms and frequencies; (*b*) there was no consistent unilateral focus, but focal abnormalities shifted in location from time to time, or multiple foci were present simultaneously and independently in different areas of both hemispheres; (*c*) paroxysmal discharges at times became bilaterally synchronous but irregular in form and frequency.

TABLE 1.—*Summary of Clinical Data*

	Total Series	Focal Anterior Temporal	All Other Focals	Hemispheral	Bilateral Synchrony	Diffuse Dysrhythmias
Total no. of patients, %	100	30	28	11	18	13
Males, %	44	42	41	42	44	58
Average age at onset of seizures, yr.	8	12	7	4	10	5
Average age at first visit to Department of Neurology, yr.	14	20	11	10	15	9
Etiological factors (total no.)						
Concussion	20	9	7	--	2	2
Contusion	9	1	4	2	--	2
Meningitis	3	2	--	--	--	1
Proved encephalitis or abscess	12	4	--	4	--	4
Suspected encephalitis	8	3	3	--	2	--
Congenital syphilis	1	--	1	--	--	--
Definite birth trauma	14	1	5	7	--	1
Suspected birth trauma (cyanosis, prolonged labor, or prematurity)	27	4	14	--	1	8
Severe postnatal jaundice	3	--	2	--	--	1
Embolus	1	--	1	--	--	--
Hypertensive encephalopathy (due to nephritis or eclampsia)	2	1	--	--	--	1
Congenital malformations (hydrocephalus, encephalocele)	4	1	1	1	--	1
Seizures followed by hemiplegia	10	--	--	10	--	--
Definite organic etiology (all the above, except concussion, suspected encephalitis, and suspected birth trauma), %	26	14	22	100	0	35
Abnormal neurologic examination, %	21.5	10	16	100	0	26
Mental retardation, %	20	9	22	50	5	39
Patients with positive family history, %	36	30	43	43	37.5	29
% of seizure types						
Minor only	18	22	13	21	19.5	16
Major only	17	13	20.5	12	24.5	10
Minor and Major	65	65	66.5	67	56	74

Clinical Data

Clinical data in this series of 228 patients are summarized in Table 1. The patients with focal abnormalities in the electroencephalogram form the largest group, more than all other combined, and the majority belongs to the focal anterior temporal group. Comparing this with Gibbs' extensive material,[11] we noted that in our series the patients with focal electroencephalographic abnormalities (all focal and hemispheral) comprise 69% of all patients, while in his material this same group amounts to only 28%. As far as the subdivisions in these focal groups are concerned, however, our percentages correlate very closely with those of Gibbs. In Jasper's series[10] focal abnormalities were present in 52% of his epileptic patients, with over half of them localized in the temporal lobe.

In the group with bilateral synchrony the number of patients with different types of seizures was quite small (5 with petit mal only, 12 with petit mal and grand mal, 9 with grand mal only, 1 with myoclonic seizures, 5 with myoclonic and grand mal seizures, 2 with akinetic seizures, 2 with transient episodes of confusion, and 5 with transient episodes of confusion and grand mal seizures).

The average age at onset of seizures is highest in the group with bilateral synchrony and the focal anterior temporal group; this has been noted before in the literature.[11] It is lowest in cases with hemispheral abnormalities and diffuse dysrhythmias.

The average age of the patients at the first visit to the Department of Neurology

TABLE 2.—*Relation of Age to Convulsive Disorders*

	Age Groups		
	Under 12 Yr.	12-20 Yr.	Over 20 Yr.
Age at onset of seizures	169	33	26
Age at first visit to Department of Neurology	128	41	59

is recorded in Table 1. Table 2 shows the number of patients in various age groups. It may be seen from Table 2 that the majority of patients were under 12 years of age.

The percentages of patients with a history indicative of organic etiology, with abnormal neurologic examination, and with mental retardation are highest in the groups with hemispheral abnormalities and diffuse dysrhythmias. The percentages of these same factors are low in the group with bilateral synchrony, indicating that this group consists predominantly of patients with primary bilateral synchrony or centrencephalic seizures.[10]

The various etiologic agents have been listed in Table 1: Concussion prior to onset of seizures; suspected encephalitis, not proved by spinal fluid examinations, and suspected birth trauma, as in the case of prolonged labor, premature birth, or transient postnatal cyanosis, have not been accepted as indicating a definite organic etiology.

Abnormal neurologic findings include only those signs referable to hemispheral or bilateral cerebral damage and are represented by pyramidal tract signs, hemisensory findings, visual-field changes, and choreoathetosis. Other findings not related to damage of one or both cerebral hemispheres, such as optic atrophy, strabismus, and deafness, have not been included. Mental retardation has been accepted as present only when substantiated by psychological tests.

The percentage of patients with positive family history is approximately the same in all groups, a finding which has been reported previously.[11] We were struck by the rather high incidence of a positive family history in the hemispheral group. In this group there were 10 patients whose hemiparesis seemed to have resulted from increasingly severe seizures in childhood without other etiologic factors (as may be seen in Table 1): Of these 10 patients, 6 had a positive family history; 3, a negative one, and for one no definite family data were available. This very high incidence of positive family history leads to speculation that we might be dealing here with a strong tendency toward seizures, with severe seizures in childhood, resulting in brain swelling, herniation, anoxia, and hemiparesis.

The seizures were divided according to type into minor only, major only, or a combination of minor and major seizures. We have defined major seizures as associated with loss of consciousness and falling (with, however, an occasional exception, such as akinetic seizures, which were considered as minor seizures) and minor seizures as associated with absence of complete loss of consciousness and falling (with an occasional exception, as in petit mal, which was considered as a minor seizure, even though transient complete loss of consciousness is present). It may be noted that most patients suffered from a combination of minor and major seizures.

Result of Treatment

The response to treatment in the individual patient was rated as follows:

A: 100% controlled:	Seizures completely controlled for at least one year, if the original frequency was more than one seizure a week, or for at least two years, if less frequent
B: Almost controlled:	Seizure frequency reduced by at least 90%
C: Improved:	Results intermediate between B and D
D: No improvement:	Seizures increased in frequency or severity, or remaining the same, or less than 50% improvement

The results in the total series of patients and in the separate categories are listed in Table 3, both in total number and in percentages. Results are more simplified in Table 4, in which the total number of patients in D is compared with the total number in A and B, as the most significant responses, and an index of favorable outcome is calculated by dividing (A+B) by D. Table 5 schematically represents the prognosis in different categories, as obtained from this index.

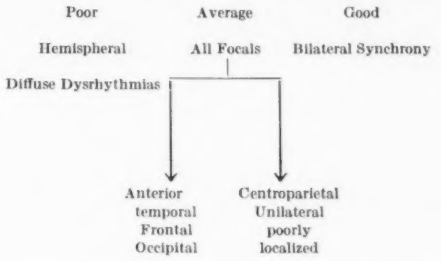
TABLE 3.—*Result of Treatment*

	No. of Patients	No Result	50%-90% Improved	Almost Controlled 90%-100%	100% Controlled	Attempted Reduction of Medication: Result	Additional Comments
Total series	228	30% (68)	12% (27)	20% (47)	38% (86)	41 : 19 unsuccessful 6 stopped all medication	
Focal anterior temporal	69	29% (20)	17½% (12)	27½% (19)	26% (18)	9 : 5 unsuccessful 3 stopped all medication	Of the 20 uncontrolled patients, 7 underwent temporal lobectomy: 1 unsuccessful & hemiparesis 3 seizures improved 3 controlled & reducing
Focal frontal	15	27% (4)	20% (3)	13% (2)	40% (6)	4 : 2 unsuccessful	
Focal centroparietal	19	16% (3)	0% (0)	16% (3)	68% (13)	6 : 2 unsuccessful 1 stopped all medication	
Focal posterior temporal	16	19% (3)	12% (2)	25% (4)	44% (7)	5 : 2 unsuccessful	
Focal occipital	7	43% (3)	0% (0)	14% (1)	43% (3)	2 : 2 unsuccessful	Of the 3 uncontrolled patients: 1 died in status epilepticus 1 underwent occipital gyrectomy and improved
Focal unilateral poorly localized	6	17% (1)	0% (0)	33% (2)	50% (3)	2 : 1 unsuccessful	
Hemispheral	24	58% (14)	17% (4)	8% (2)	17% (4)	1 : 1 unsuccessful	Of the 18 patients who were uncontrolled or improved, 6 had hemispherectomy: 1 died after operation 4 controlled & off all medication 1 controlled & reducing One other patient had focus excision without result
Bilateral synchrony	41	12% (5)	7½% (3)	17% (7)	63½% (26)	9 : 3 unsuccessful 1 stopped all medication	
Diffuse dysrhythmais	31	48% (15)	10% (3)	23% (7)	19% (6)	3 : 1 unsuccessful 1 stopped all medication	One uncontrolled patient underwent hemispherectomy and frontal lobectomy on the opposite side, without result

TABLE 4.—*Result of Treatment*

	No Result (D)	Controlled (A) + Almost Controlled (B)	(A+B) : (D)
Total series	68	133	2
Focal anterior temporal	20	37	1.85
All other focal	14	44	3.1
Hemispheral	14	6	0.4
Bilateral synchrony	5	33	6.6
Diffuse dysrhythmias	15	13	0.9

TABLE 5.—*Result of Treatment*



It is evident from these data that in this series the best result was obtained in the patients whose electroencephalographic abnormalities showed bilateral synchrony. The electroencephalographic criteria and the clinical data indicate that this group would usually be considered as suffering from idiopathic epilepsy. The worst results are in those with EEG's classified as hemispheral and as diffuse dysrhythmias: In these groups we found the highest number of patients with definite organic seizure etiology, with abnormal neurologic examinations, and with mental retardation. Results in patients whose electroencephalograms showed focal abnormalities are in between, but there seems to be a difference in prognosis depending on the location of the focus. Table 3 suggests that patients with a centroparietal focus obtain much better results than those with a frontal, occipital, or anterior temporal focus, though the number of patients in some of these categories is too small from which to draw valid statistical conclusions. Similar results are, however, reported in the literature.[3]

Factors of Significance in Determining Prognosis

For statistical evaluation and comparison of different factors, two groups were compared in each single instance: poor results (all D's) against good results (A and B). The group with 50%-90% improvement (C) was not considered in statistical evaluation. Results are tabulated in Table 6.

It may be seen that in the total series prognosis was significantly worse when seizures started before the age of one year, when there was a definite organic etiology, when there was an abnormal neurologic examination, or when the patient was mentally retarded. This is probably related to the fact that the prognosis in the groups with hemispheral abnormalities and diffuse dysrhythmias is poor, for it is in these groups that (according to Table 1) one finds the lowest average age of onset and the highest percentage of organic etiology, abnormal neurologic examination, and mental retardation.

Another factor of significance in the total group (and to a less degree also in some of the separate categories) is the type of seizures. Patients with only major seizures have a better prognosis, and the percentage reduction of seizure frequency is not influenced by the initial frequency of major seizures: The number of patients showing seizure reduction of 90% or better was approximately the same in those who started with a large number of major seizures as it was in those who initially had few. Seizure frequency, as far as minor seizures are concerned, however, does play a definite role in determining prognosis: If the initial seizure frequency is high, less response to treatment may be expected.

It can be seen from Table 6 that the interval before treatment is started is only questionably significant, as is the incidence of positive family history.

TABLE 6.—*Prognosis as Related to Different Factors* *

	Total Series	Focal Anterior Temporal	All Other Focal	Hemispheral	Bilateral Synchrony	Diffuse Dysrhythmias
Sex	—	—	—	—	—	—
Age at onset of seizures	Worse, if under 1 yr. +++	—	—	—	—	Worse, if under 1 yr. ?
Interval before treatment was started	Worse, if longer than 1 yr. ?	Worse, if longer than 1 yr. ?	—	Worse, if longer than 1 yr. ?	—	—
Family history	Better, if positive ?	—	—	—	Better, if positive ?	—
Etiology	Worse, if definitely organic ++	Worse, if definitely organic ?	—	— †		—
Neurologic examination	Worse, if abnormal +++	Worse, if abnormal +	—	— †		—
Mental retardation	Worse, if retarded +++	—	Worse, if retarded ?	—	—	Worse, if retarded ?
Type of seizures	Better, if only major +++	—	Better, if only major +	—	—	Better, if only major ?
Time of day of seizures	—	—	—	—	—	—
Seizure frequency						
Minor	Worse, if more than 1/wk. +++	—	Worse, if more than 1/wk. ?	—	—	Worse, if more than 1/wk. +
Major	—	—	Worse, if more than 1/mo. ?	—	—	—
Relation of seizures to menstruation	—	—	—	—	—	—
Degree of EEG abnormality		—	—	—	—	—

* —=*P* more than 0.05; ?, *P* 0.05-0.02; +, *P* 0.02-0.01; ++, *P* 0.01-0.001; +++, *P* less than 0.001.

† Nature of etiology and degree of hemiparesis had no influence.

Sex, time of day of seizures, relation of seizures to the menstrual periods, and the severity of electroencephalographic abnormality in the various subgroups have no influence on prognosis.

It must be stated, however, that the number of different electroencephalographic abnormalities in the group with bilateral synchrony was too small from which to draw valid statistical conclusions.

In the focal groups we have divided electroencephalographic abnormalities into three categories: (1) a strictly focal spike or sharp wave; (2) a strictly focal spike or sharp wave with an occasional synchronous or independent spike or sharp wave in the identical contralateral brain region; (3) bilateral and generalized spike or spike and slow-wave discharges with focal preponderance and focal phase reversal. There was no significant statistical difference in the prognosis in these three categories.

In the hemispheral group it did not make any difference in which area of the brain the maximal abnormal discharge was localized, or whether there was spread of the abnormal discharge to the contralateral side or not.

A statistically significant difference is more difficult to obtain in a smaller series of patients, and this may be one of the reasons that less significant factors were present in the separate groups than in the total series.

Medication

The patients were treated with various medications in an attempt to control seizures. Sometimes this was achieved easily; if not, then other medications were tried in an effort to achieve better results. Among the medications that were successful in the controlled and almost controlled groups (A and B), diphenylhydantoin (Dilantin) and phenobarbital were found to be the outstanding and most frequently used drugs in the total series and in all individual groups. Trimethadione (Tridione) was equally outstanding only in the group with bilateral synchrony.

Occasional additional benefit in all groups was derived from primidone (Mysoline), methylphenylethylhydantoin (Mesantoin) or methsuximide (Celontin). Trimethadione was sometimes helpful in cases classified as "other focal," hemispheral, and diffuse dysrhythmia. Paramethadione (Paradione) was sometimes helpful in the groups with bilateral synchrony and diffuse dysrhythmias, and phensuximide (Milontin) occasionally in the group with bilateral synchrony.

Attempts to Reduce Medication After Complete Control

The relevant data are recorded in Table 3. Of the 86 completely controlled patients, 41 tried to reduce medication: Of these, 19 had a recurrence of seizures or aura; 6 could discontinue all medication, and 16 are still in the process of gradually reducing their medications. Merritt [12] reported on 89 controlled patients who reduced medication: Of these, 29 achieved complete withdrawal without recurrence of seizures, and 39 were unsuccessful.

Successful withdrawal of medication may be related to the disappearance of electroencephalographic abnormalities, once the seizures are controlled. This seemed to be the case only in the group with bilateral synchrony. Nine patients tried reduction. Three were unsuccessful, and in each instance the electroencephalogram was still abnormal after complete control of seizures had been achieved. In the one patient who tolerated discontinuation of all medication, the electroencephalogram had become normal after control of seizures. The other five are still in process of reducing medication: Only one continued to have an abnormal electroencephalogram.

In the other categories, however, such correlation was not present. In the focal anterior temporal group, for instance, nine tried reduction. In five the electroencephalogram still showed focal abnormalities; three were unsuccessful, but one was able to stop all medication. The other four had a normal electroencephalogram when seizures were

controlled: Two failed in their attempt at reduction; two were able to stop all medication. A similar situation was present in the other focal groups.

Surgery

Surgical procedures are reported in the last column of Table 3. Surgery was mostly performed on uncontrolled patients in the focal anterior temporal and hemispheral groups. These categories, according to Tables 4 and 5, show a rather poor response to treatment, but the results of surgery are often excellent (as can also be seen from our small series in Table 3). Thus, anterior temporal lobectomy and hemispherectomy may be powerful tools in improving prognosis in these two groups.

Summary

Data in the literature concerning the long-term prognosis in convulsive disorders are scarce, as most studies deal with the short-term response to one particular anticonvulsant medication. In long-term studies the percentage of completely controlled patients ranges from 26 to 75. This is probably caused by differences in type of patients and type of seizures in the various series.

In the present article an attempt was made to define which factors are of significance in determining prognosis. A total of 228 patients were studied; these had been followed for an average of 4.7 years per patient and had had an average of 3.3 electroencephalographic examinations performed per patient. The patients were divided in groups, according to purely electroencephalographic criteria. Clinical data are presented in Tables 1 and 2. The results of treatment are presented in Tables 3, 4, and 5. The best response was observed in patients with bilaterally synchronous paroxysmal discharges in the electroencephalogram. This group usually would have been classified as suffering from idiopathic epilepsy. Prognosis was poorest in the hemispheral group (in which the electroencephalogram showed abnormalities originating in one hemisphere and appearing over the entire hemisphere, without being restricted to one particular region) and in patients with diffuse dysrhythmias (with bilateral paroxysmal discharges, as well as abnormal focal discharges appearing independently in different areas of both hemispheres, and an almost continuous abnormal interseizure record). In these last two groups onset of seizures was earlier than in other groups; there was also a high incidence of definite organic etiology, abnormal neurologic examination, and mental retardation. The focal groups were in between as far as prognosis is concerned, but patients with a centroparietal focus showed better results than those with frontal, anterior temporal, or occipital foci.

In the total series prognosis was significantly worse when seizures started before the age of one year, when there was a definite organic etiology, when there was an abnormal neurologic examination, or when the patient was mentally retarded. Patients with only major seizures had a better prognosis, and the initial frequency of major seizures had no influence on the ultimate outcome as far as percentage reduction in seizures was concerned. In patients with minor seizures, however, it was noted that a high initial seizure frequency would adversely influence prognosis.

The duration of the disorder prior to onset of treatment and the incidence of positive family history were only questionably significant as regards prognosis, and no influence could be attributed to sex, time of day of seizures, or relation of seizures to the menstrual period.

These various factors are presented in detail in Table 6.

Diphenylhydantoin and phenobarbital were found to be the most consistently valuable medications. Of the 86 completely controlled patients, 41 attempted gradual reduction of medication: Of these, 19 experienced a recurrence of seizures or aura, 6 tolerated discontinuation of all medications, while 16 are still proceeding with gradual

reduction. Patients with bilaterally synchronous abnormalities in the electroencephalogram seemed to tolerate withdrawal of medication better when control of seizures had resulted in a normal electroencephalogram. This was not found to be true for other groups.

Attention is again drawn to anterior temporal lobectomy and hemispherectomy as powerful therapeutic tools in a select and limited number of cases.

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Posterior Interosseous Nerve Palsy with Spontaneous Neuroma Formation

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Although paralysis of the posterior interosseous nerve is relatively unusual, there has been over the years a large measure of uncertainty about the nature of the causative lesion. In the literature, there is a paucity of pathologic proof about this disorder. The purpose of this paper is to demonstrate a specific causative lesion capable of producing such paralysis, to elucidate the pathologic processes which are very likely causative in many cases, and to demonstrate the recovery which may follow definitive surgical correction of the offending lesion.

Anatomy and Function

After the radial nerve gives off its branches to the extensor carpi radialis longus and the extensor carpi radialis brevis, it enters the antecubital fossa on its lateral aspect between the biceps and brachialis, medially, and the brachioradialis, laterally. It then divides into a superficial (sensory) branch and a deep, or posterior, interosseous branch, which has a very short course before it passes posteriorly through the substance of the supinator (brevis) muscle, to wind around the neck of the radius, and then down deep in the dorsal region of the forearm along the interosseous membrane. This branch supplies the extensor carpi radialis brevis, supinator, extensor digitorum communis, extensor digiti quinti, extensor carpi ulnaris, abductor pollicis longus, extensor pollicis longus and extensor pollicis brevis, and the extensor indicis proprius. The nerve has no sensory function. Thus, lesions of this nerve cause loss of function of the innervated muscles without any sensory loss.

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Review of Literature

Progressive nontraumatic paralysis of the posterior interosseous nerve has not been reported very often, but even more significant is the relative lack of pathologic evidence of the actual lesions involved in this disorder. A very good survey of the literature appeared in March, 1958, by Hustead, Mulder, and MacCarty,[1] reviewing 16 cases reported variously elsewhere and adding 2 cases of their own. This revealed a total of seven operative cases. Two were reported as enlargements of the bicipitorial bursae with compression of the adjacent nerve. Three were lipomata in the antecubital fossa with the same mechanism. One case had an anomalous course of the nerve, superficial to the supinator muscle, with assumed compression of the nerve by the overlying extensor aponeurosis. Finally, Otenasek's[2] case, reported in 1947, was reviewed. In this case, there was a proved fibroma, 2 mm. in diameter, of the posterior interosseous nerve trunk. Resection and end-to-end anastomosis were accomplished, but without any functional return at the end of two years.

Since the review of the literature by Hustead et al.,[1] three additional cases have been reported up into 1958. Campbell and Wulf[3] reported a case of paralysis caused by compression of the nerve by a lipoma beneath the supinator muscle. Another case of compression by a lipoma was reported by Cappellini.[4] Finally, and most significantly, there was a report in 1958 by Kruse[5] concerning a spontaneous, complete recovery

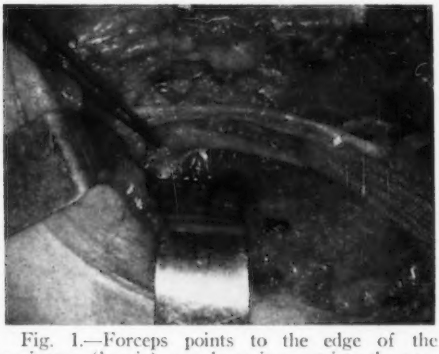


Fig. 1.—Forceps points to the edge of the supinator (brevis) muscle as it constricts the posterior interosseous nerve. The neuroma is to the left of the forceps. The tape at the far left is on the common radial nerve. The superficial (sensory) branch lies below the neuroma.

Fig. 2.—The neuroma is more obvious after transecting the fibers of the upper medial edge of the supinator muscle (between the retractors).

over eight months' time in a woman whose paralysis began rather acutely, following excessive swimming, and rapid progression over four days' time. In this patient there was severe pain and stiffness in the elbow at the time of onset. Kruse attributed her disorder to possible bursitis in the antecubital fossa with involvement of the contiguous dorsal interosseous nerve.

Report of a Case

The patient was a 45-year-old white bartender who, without prodrome or trauma, noted the insidious onset of weakness in extension of the left index finger, three years prior to his admission to Jefferson Medical College Hospital in 1957. Three months after onset, there was weakness of extension of the left thumb, which he noted while counting paper money. Nine months after onset, he experienced dragging of the ring and little finger of his left hand while combing his hair. Two years after onset, he noted beginning atrophy of the left forearm and a tight, pulling sensation in the antecubital fossa. The problem was complicated by periodic pains in the occipital and posterior cervical areas, especially on the left side, over those same three years. He described these pains as spasms, lasting from 30 to 60 minutes, relieved by rest, and occurring once every two or three months.

His past medical history, social and occupational history, and system review were all noncontributory.

Fig. 3.—Cross section of neuroma. There is abundant overgrowth of perineural and endoneural connective tissue. The Schwann-cell nuclei are increased in number. Myelin is markedly reduced. Hematoxylin and eosin; 10× objective.

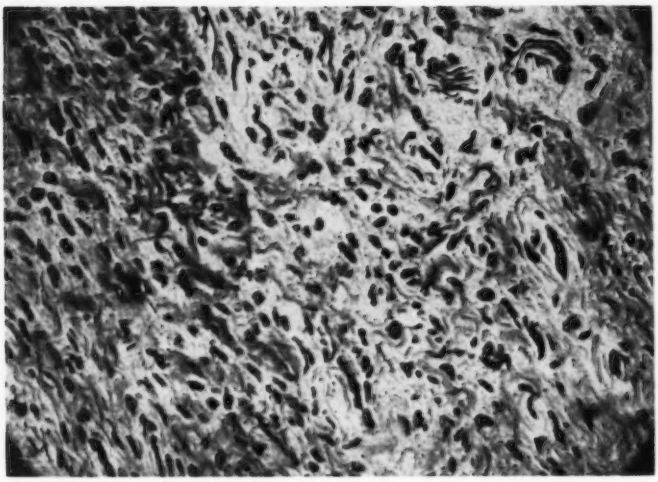


Fig. 4.—Tangential section of neuroma. Axon fragments and proliferating neurites are tangled among the increased number of Schwann-cell nuclei. Bodian protargol stain; 40 × objective.

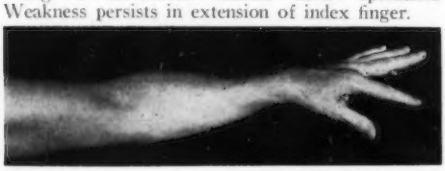
Examination revealed point tenderness over the lateral aspect of the left antecubital fossa and a suspicion of a small mass in this location. There was painful limitation of extension, adduction, and internal rotation of the left arm, the pain being referred to the antecubital fossa. There was marked atrophy of the muscles of the dorsum of the left forearm. There was weakness of extension of the fingers of the left hand, with relative sparing of the middle finger. There was no weakness at the wrist.

Hemogram, urinalysis, fasting blood sugar, blood serology, and spinal fluid studies were all normal. The chest x-ray was normal. The cervical spine x-ray showed minimal degenerative arthritis. An x-ray of the left shoulder revealed minimal calcification in the insertion of the left supraspinatus tendon. Electromyography was confusing in that the examiner interpreted the test as revealing incomplete interruption in the left median and ulnar nerves and noted minimal involvement in the muscles of the right upper arm.

Surgical exploration of the left antecubital fossa was performed on April 17, 1957. Just as the posterior interosseous branch of the radial nerve escaped through the supinator muscle, there was seen a large neuroma, the entirety of which was actually distal to the upper medial edge of that muscle, this point being, apparently, a point of constriction against the nerve. Transection of the fibers of that muscle revealed what appeared to be a neuroma in continuity, a lesion 1.5 cm. in length by 0.5 cm. in diameter. The nerve mass, therefore, was situated between the supinator muscle and the neck of the radius. Both sinusoidal and faradic currents were used to stimulate the nerve. Such stimulation proximal to the lesion resulted in only mild extension of the middle finger, but stimulation distal to the lesion produced appropriate, although weak, muscular responses in the hand. By adducting the arm toward the chest, flexing it at the elbow, and freeing up the radial nerve proximally in the upper arm, it was possible to attain sufficient relaxation to resect the lesion and perform primary anastomosis. No major branches of the nerve were sacrificed. The arm was fixed to the chest wall with a plaster cast, which was removed eight weeks later. At that time, there was complete loss of function of the affected nerve.

The patient was last seen for a follow-up examination in September, 1958, or 17 months after operation. There was complete restoration of function in the left hand, with the exception of index-finger extension, which had only partially returned. The atrophy of the forearm had disappeared. There was, of course, no sensory loss in the hand. The patient had no working disability.

Fig. 5.—Seventeen months after operation. Weakness persists in extension of index finger.



Comment

The nerve lesion was reported histologically by Dr. Richard Berry as a neuroma, consisting of proliferation of connective tissue and multiple tangled neurites, as seen in

a typical traumatic neuroma. It is interesting to compare with this lesion the one resected by Otenasek,[2] in 1947, since his case was the only other one reported similar to ours. That lesion was found just distal to the origin of the posterior interosseous nerve and apparently was not related to the supinator muscle. It was reported as being "largely composed of connective tissue, which is very cellular, and also contains many collagen fibers. . . . The lesion differs from a neuroma in that it consists chiefly of a new growth of connective tissue. . . . It seems probable that it is a fibroma." Otenasek further commented: "The unique anatomical course of the nerve through the supinator muscle has led to the assumption that some mechanical factor involved in this muscle-nerve relationship has resulted in the loss of function of the nerve." The pathogenesis in our case can only be conjectural, but it is difficult to apply Otenasek's concept in view of the rarity of this lesion. Moreover, in our case, there was no evidence of exogenous trauma, inflammation, or intoxication as an etiologic factor. It is likewise difficult to believe that the cervical arthritis (which was also symptomatic) could have caused some sort of spasm of the supinator muscle with irritation of the underlying nerve. Nevertheless, this and other case reports demonstrate the multicentric origin of paralysis of the posterior interosseous nerve, apart from direct trauma, namely, bursitis, anomalous nerve pathway, lipomata, and actual neuroma or fibroma formation in the nerve itself.

Summary

We have reported a case of paralysis of the posterior interosseous nerve due to neuroma formation in the nerve, and it is suggested that, in all probability, many other patients will be found to have the same lesion, especially in view of the occurrence of point tenderness in the antecubital fossa just over the nerve trunk. We have also demonstrated the restoration of function following resection and end-to-end anastomosis. The literature has been reviewed and brought up to date. It is recommended that, in view of the fact that only one case with spontaneous recovery in such a lesion has been reported, and in view of the therapeutic possibilities, surgical exploration should be performed in all cases of progressive paralysis of the posterior interosseous nerve.

111 N. 49th St. (Dr. Alpers).

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Obituaries

LEE McKENDREE EATON, M.D.

1905-1958

Lee Eaton, my friend of 24 years, Professor of Neurology in the Mayo Foundation, Graduate School of the University of Minnesota, and Chairman of the Sections of Neurology of the Mayo Clinic, died suddenly last November.

As president of the Association of Research in Nervous and Mental Diseases, he had worked for a year in arranging the 38th annual meeting of the Association, devoted to neuromuscular disorders. The current volume of the association has been dedicated to his memory for his leadership and his intensive research activities in this field.

I find myself reluctant to detail in cold outline the substance of his more than 50 published papers, and, moreover, the many honors he had won in his profession, for I do not feel that Lee would like it so. Rather, I should like to recall some facets of the personal and medical philosophy of this simple, yet complex, man.

The bedrock of his personality was that of a tender devotion to his family and an unswerving dedication to his patients, his profession, and his colleagues. On this solid base sparkled the rich and varied gems of his enthusiasms, and his zestful love of living.

In 1938 he became convinced that the fields of psychiatry and neurology were in many ways opposing disciplines, and from that time on he anticipated and prophesied the current explorations in the physiochemical, conditioned, and genetic nature of the human psyche. He was a practitioner of somatopsychic medicine during the period when both physicians and patients were devoting more and more attention to the psychosomatic aspects of disease.

We who have worked with him have seen him establish and prove a diagnosis of myasthenia gravis in a so-called neurotic patient on the basis only of the presenting symptoms and the single clinical finding of a "weak little finger." In the no-man's land between body and spirit he found myxedema in depressions, encephalitis in dementia precox, tumors of the frontal lobe in abnormalities of behavior, and bizarre forms of epilepsy in hysteria. If there was an organic explanation of a patient's disability, it was deftly uncovered by the probe of his questioning and the tools of his examination. These techniques and methods he outlined as both editor and contributor in "Clinical Examinations in Neurology," published as a textbook in 1956.

The contrasts of his life were fascinating.

He was a college student in the "roaring twenties," and an intern and Fellow during the following depression. Over his desk hung a picture to remind him of his goal and how he should find it. It was a representation of a northern pike, and under it was the motto: "Any old fish can drift along and dream. But it takes a real live one to swim against the stream."

The inclination of this professor of neurology was to drift down his beloved Mississippi River in a houseboat, with a gun, a trotline, and an earthenware crock.

And yet he faced upstream all his life, breasting the constant demands of patients, students, and family. He did this without wavering or compromise in time or effort, for he had dedicated himself to each.

Lee Eaton, the professor, was a superb teacher, direct and as homely as an old-fashioned quilt and just as colorful. At the same time he incessantly sought information about everything that moved or grew or was hidden on the face of the earth. He was a perpetual student. I think this is best illustrated by the remarks made by an island physician, when, in 1954, Lee traveled through Hawaii, New Zealand, and Australia. The physician, who had followed him for days as he had examined and recorded flora, fauna, and the artifacts of man, said: "You would think that he was the very first explorer to have ever visited these shores."

Somehow or other he found time for everything. He established three Sections of Neurology. He could fill a hunter's pot with duck and pheasant, play poker with friendly cutthroats, make with his own hands the furniture of a home, and develop photographic prints with expert skill. In all these activities his family shared. He taught his wife and boys and girls to hunt and fish, and he took them on expeditions up and down the big river.

Here was an inveterate and stalwart Midwesterner who could be and was a social intimate of farmers, roustabouts, and the river people—a man who could talk their language. Yet he was respected in the drawing and consultation rooms of the elite on both coasts of this continent, and in the fabulous world down under.

In his 53 years he lived several lifetimes. The shock of his death is softened by our knowledge that he had done everything in life worth doing, and in the doing had never been unkind.

He is survived by his lovely wife and companion, the former Mary Louise Long; and his children, Mrs. Elizabeth D. Monson, Lynne St. Pierre, Emily Jordan, Charles McKendree, and Thomas Lee.

ALEXANDER R. MACLEAN, M.D.

Society Transactions

PHILADELPHIA NEUROLOGICAL SOCIETY

James J. Ryan, M.D., Presiding

Regular Meeting, March 7, 1958

An Unusual Space-Taking Lesion of Pons.

Dr. Michael Scott and Dr. Alexander Silverstein.

A case is reported of a midline intrapontine cyst which pointed through the floor of the upper fourth ventricle and which on surgical evacuation yielded yellow fluid that clotted spontaneously. The condition over many months suggested multiple sclerosis. There was bilateral involvement of the medial longitudinal fasciculus, with sparing of the nerves supplying the extraocular muscles. The corticobulbar tracts supplying the cranial nerves were completely spared. The pyramidal tracts to the upper extremities were slightly involved as compared with the profound involvement of the pyramidal tracts to the lower extremities. Since the fibers for the upper extremities supposedly are more mesial than those for the lower, one would expect the reverse.

Another unusual feature was the position of the fingers, viz., flexion of the proximal phalanges and extension of the terminal phalanges. The present alertness and awareness and the relative freedom from prolonged sleep are difficult to explain in view of a large lesion in part of the reticular formation. The retention of corneal pain and temperature sensation can be explained by the laterality of these tracts, and the sparing of hearing, by the position of the lesion in the upper pons. The etiology of the cyst is obscure. Since the patient has slowly improved for the past 14 months, we favor a posthemorrhage cyst rather than tumor. A large vascular anomaly or aneurysm has been ruled out by the vertebral angiogram, and a blood dyscrasia, by numerous studies. The patient has been normotensive except for an elevated blood pressure before the onset of his illness. A small angiomatous lesion is a possibility.

Discussion

Dr. Nathan Schlezinger: I would like to ask, Dr. Scott, whether this lesion could have been an astrocytoma.

Dr. Michael Scott: No, because for 18 months since the operation he has been improving. There has been no x-ray therapy and no change in the position of the silver clips, which would shift if a tumor were enlarging.

Dr. Joseph A. Brady: Would a syringobulbia cavity go this high? A lesion in the midline structure is usually cystic in type.

Dr. Arthur B. King: If it were syringobulbia, the fluid protein would not be so high.

Dr. Robert Groff: Normally, fluid from a syringobulbia cavity does not jell. The fluid that Dr. Scott removed jelled promptly.

Dr. Nathan Schlezinger: Is there a permanent opening in the cyst?

Dr. Michael Scott: I don't know. There is no choked disc or recurrent blockage. If the cyst is still open into the fourth ventricle, it is not putting out increased protein, because repeated spinal taps show the normal amount. I wish that I had thought at operation of instilling a few drops of iophendylate (Pantopaque) into the cyst.

Dr. Robert Groff: Perhaps it is just as well that you did not do so. The irritation might have been marked.

Dr. Arthur B. King: It is possible that this lesion may have been an angioma developing slowly over a long time.

Dr. Alexander Silverstein: It is interesting to note that Dr. Scott cut through the floor of the fourth ventricle in order to empty the cyst. Before and immediately after the operation, the patient presented the clinical picture of marked destruction of the brain stem. There were quadriplegia, aphasia, and anarthria, and even three months after the operation there was still evidence of alterations in consciousness, and marked somnolence. For example, after trying to answer questions for about 10 minutes, he would drop off in a deep sleep. The loss of upward associated eye movements would indicate involvement of periaqueductal gray matter in the midbrain. Of interest was the flaccid paralysis of both lower extremities, which was still complete after 18 months. There was absence of deep reflexes, and extensor plantar responses were not elicited. As to diagnosis, the improvement in this patient would be in favor of the diagnosis of vascular lesion such as hemorrhagic cyst, especially since one of the earliest

symptoms was hypertension. However, an astrocytic cyst cannot be altogether excluded.

Neurologic Aspects of Ataraxic Drug Therapy. DR. N. WILLIAM WINKELMAN JR.

Two great discoveries made in recent years are described: (1) the function of the reticular formation of the brain stem (1937, with gain in momentum since 1947), and (2) the investigation of the action and clinical uses of the phenothiazine derivatives (1953). This paper is a review of the historical development of present knowledge concerning the reticular formation and its importance in the field of new drugs. The use of phenothiazine derivatives is discussed in the treatment of convulsive states, abnormal involuntary movements, painful conditions, and increased psychomotor states associated with brain disease. In the convulsive states the drug has a different use in low, moderate, and high dosages. The following topics are then discussed: undesirable actions by the drugs on the central nervous system, including extrapyramidal signs and symptoms, akathisia, and the various dyskinesias. Other subjects outlined are management of the extrapyramidal complications; dystonia; hyperthermia, epileptogenic characteristics, and deeply stuporous conditions. It is concluded that this field is one of tremendous importance for the clinical and experimental neurologists.

Discussion

DR. MICHAEL SCOTT: I enjoyed Dr. Winkelman's summary very much. What drug did you use, in addition to chlorpromazine, in cases of psychomotor epilepsy?

DR. ALEXANDER SILVERSTEIN: I wonder how many reports of the wonderful results obtained with the use of chlorpromazine came from reliable neurological research centers? I have used the drug in cases of hyperkinetic states, and I have not found that it is of benefit. Perhaps I was not using the proper dosage. Can you help me out from that viewpoint, Dr. Winkelman?

DR. N. WILLIAM WINKELMAN JR.: Most of the cases of psychomotor epilepsy reported on here were seen about four years ago. At that time the patients were taking or had taken just about everything you could name. When I added chlorpromazine, their seizures stopped. They were seen at the clinic for the succeeding three months and were free of seizures during that time. However, over the years I have lost touch with these persons and have no recent follow-up data available. In response to Dr. Silverstein's question regarding reliable neurological research centers, I must admit he has a good point. Most of these reports came from state hospitals, and many of the investigators do not specialize in neurology to as great a degree as they do in psychiatry. As far as the dosage is concerned, it is my practice to start with a low dose and build up. A patient was recently discharged on a dosage of 10 mg. t. i. d. If one gets negative results on less than 300 to 400 mg. a day, it is not a true trial of the drug. Throughout this paper you will notice that I have used the term chlorpromazine. Of these drugs, it is first in prominence, is most potent, and has less toxicity, in my experience. I am here not to try to prove the drug's worth but to report on the results obtained with its use. I have utilized this drug in activating EEG's.

Subarachnoid Hemorrhage Associated with Paraganglioma. DR. MORTON W. SHRAGER (by invitation), DR. WILLIAM B. GLANTZ (by invitation), and DR. NATHAN SCHLEZINGER.

A case of pheochromocytoma associated with subarachnoid hemorrhage and death is reported in a 14-year-old child who had previously been asymptomatic except for headaches. Eyeground examination on admission revealed early changes of papilledema. Hypertension was present but was not a prominent part of the clinical picture on admission. A review of the literature reveals that neurological symptoms are prominent presenting complaints in most cases of pheochromocytoma reported in children. Headache, impaired vision, convulsions, and unexplained loss of consciousness are common symptoms in children. Among physical signs, ophthalmoscopic examination revealed hypertensive eyegrounds in 84% of children reported. An increased index of suspicion, an alertness for neurological symptoms, and routine checking of blood pressure and eyegrounds in patients with these symptoms will increase the accuracy of diagnosis of pheochromocytoma in children. Finally, pheochromocytoma is discussed as a rare cause of spontaneous subarachnoid hemorrhage and of sudden death.

Discussion

DR. NATHAN SCHLEZINGER: This case presented a dramatic situation, with survival for a few hours. Without a postmortem examination, no one could have guessed that the lesion was a paraganglioma. In this particular case necropsy proved the diagnosis to be altogether different than that which was expected.

Abstracts from Current Literature

EDITED BY BERNARD J. ALPERS, M.D.

Physiology and Biochemistry

THE FLUOROMETRIC MEASUREMENT OF DEOXYRIBONUCLEIC ACID IN ANIMAL TISSUES WITH SPECIAL REFERENCE TO THE CENTRAL NERVOUS SYSTEM. J. M. KISSANE and E. ROBINS, J. Biol. Chem. 233:184 (July) 1958.

Deoxyribonucleic acid is measured in the central nervous system by a method specific for it, as opposed to ribonucleic acid. It is based on fluorescent measurement of the product of the reactions between 3,5-diaminobenzoic acid dihydrochloride and deoxyribose. The reaction is a modification of the Doebner-Miller quinaldine synthesis. The method yields values in close agreement with those based on ultraviolet absorption. As little as 0.2μg. to 3μg. of frozen-dried brain samples yield adequate analytical results. Therefore, single samples of relatively homogeneous architecture and of a size easily dissected from frozen-dried microtome sections are usable.

PAGE, Cleveland.

STUDIES OF WHITE MATTER: I. CHEMICAL CONSTITUTION AND RESPIRATION OF NEUROGLIAL AND MYELIN ENRICHED FRACTIONS OF WHITE MATTER. R. S. KOREY, M. ORCHEN, and N. BROTZ, J. Neuropath. & Exper. Neurol. 17:430 (July) 1958.

The authors devised experiments which were designed to dissect in a fashion the myelinated axon from the soma and severed processes of the glia cells. They then studied these several components with respect to each other and the parent white matter by a special process, determining nucleotides and lipid compounds and making respiration studies.

The respiration of the white matter and the fraction derived from it suggest that in homogenates about one-third of the total respiration is due to the axoplasmic system and the remainder to the cellular components of white matter.

AIGNER, Rochester, Minn.

STUDIES IN WHITE MATTER: II. ENCEPHALITOGENIC ACTIVITY OF MYELIN RICH FRACTION AND NEUROGLIAL CONCENTRATE OF WHITE MATTER. L. C. SCHEINBERG and S. R. KOREY, J. Neuropath. & Exper. Neurol. 17:439 (July) 1958.

The authors report the results of investigations to compare the encephalitogenic properties of two components of the white matter in which the pathogenic antigens may originate—one fraction as an acellular myelin-enriched component and the other as a concentrate of soma, perisomatic processes, and nuclei of neuroglial cells.

The paper was stimulated by reports by Rivers, Ferraro, Morgan, and others, who demonstrated production of experimental allergic encephalomyelitis by the injection of normal central nervous tissue alone or with adjuvants. The results indicate that the myelin-enriched fraction is capable of producing allergic encephalomyelitis, whereas neuroglial concentrates cannot initiate these changes.

The lesions produced showed histopathologic changes characterized by meningitis, focal inflammatory lesions, and demyelination. It was felt that the relative chronicity in their experiments was a feature which facilitated the appearance of demyelination.

AIGNER, Rochester, Minn.

Neuropathology

DIFFUSE TRAUMATIC DEGENERATION OF THE CEREBRAL GRAY MATTER. J. DENST, T. W. RICHEY, and K. Y. NEUBUERGER, J. Neuropath. & Exper. Neurol. 17:450 (July) 1958.

The authors report an example of diffuse cerebral cortical degeneration as a unique reaction to trauma. The case is that of a 14-year-old boy who was injured in an automobile-train accident and became comatose shortly afterward. He survived, but developed flexion contractures of the extremities, was incontinent and mute, and required a tracheotomy four months later. He developed extensive decubital ulcers and died after 10 months.

Grossly, the brain showed no evidence of crude traumatic destruction or hemorrhage. Microscopically, there was severe diffuse loss of nerve cells and astrocytic gliosis in the undisrupted cerebral cortex and selected areas of the central gray, such as the thalamus, red nucleus, and putamen on each side. The authors felt that the nature of the process bore a close relationship to cerebral concussion.

AIGNER, Rochester, Minn.

HEMIPLEGIA IN EARLY LIFE ASSOCIATED WITH THROMBOSIS OF THE SAGITTAL SINUS AND ITS TRIBUTARY VEINS IN ONE HEMISPHERE. A. DEKABAN and R. M. NORMAN, J. Neuropath. & Exper. Neurol. 17:461 (July) 1958.

Dekaban and Norman report the case of a child with hemiplegia, which began at the age of 2½ years. The child had three seizures the first day of life and another at the age of one year. Apart from these two episodes, he progressed normally until he had several seizures in succession, followed by coma for a few days and subsequent hemiplegia. After this he became mentally retarded and had almost daily seizures. The boy at the age of 12 had an I. Q. of 33. In spite of anticonvulsants he had up to eight seizures a month. He died at the age of 28.

At autopsy, the left cerebral hemisphere was found to be smaller in all aspects, with thickening of the leptomeninges. Coronal sections showed that a large part of the central region of the hemisphere, the cortex, and the centrum ovale had been replaced by spongy glial tissue containing small cavities. The sagittal sinus on microsections showed almost complete occlusion by an old thrombus. There was loss of Purkinje cells in the cerebellum. The right hemisphere was normal.

The cortical damage extended more widely than the territory drained by the system of the sagittal sinus. The extensive involvement suggested an extension of the thrombosis into the middle cerebral vein through the vein of Trolard. The changes in the occipital lobe suggested extension into the internal occipital vein. The cerebellar changes were postulated by the authors as possibly being due to part of a complete pattern of postepileptic brain damage, or to hypoxia during seizures, or associated paranatal anoxic damage, or to diphenylhydantoin (Dilantin) poisoning.

AIGNER, Rochester, Minn.

GIANT-CELL ARTERITIS INVOLVING SMALL MENINGEAL AND INTRACEREBRAL VESSELS. H. M. MCCORMICK and K. T. NEUBUERGER, J. Neuropath. & Exper. Neurol. 17:471 (July) 1958.

Giant-cell arteritis (cranial, temporal, or granulomatous arteritis) may involve vessels of the central nervous system, as possibly evidenced by fatigue, weakness, irritability, deleterious states, transient loss of consciousness, hyperreflexibility of the carotid sinus, cranial nerve disturbances, ataxia, hemiparesis, or hemiplegia.

The first case reported by the authors is that of a 52-year-old woman whose disease was not diagnosed during life. She developed headache, chills, and fever for one day. Later she had a convulsion and a temperature of 101 F. She then became somnolent, and left hemiparesis developed. Her white blood cell count was 10,250 to 14,500 per cubic millimeter, with a normal differential count. The sedimentation rate varied from 24 to 40 mm. in one hour. An exploratory craniotomy was negative. The patient improved slightly, only to have a recurrence of her condition four and one-half months later. She died nine and one-half months later. At necropsy the extracerebral arteries showed intimal thickening, with narrowing of the lumens; the destruction of the media was marked; giant cells were numerous. The smaller meningeal vessels revealed excessive endarteritis obliterans, consistent with cerebral "Buerger's disease."

The similarity of these lesions to Takayushu's syndrome, or pulseless disease, is emphasized The pathogenesis and nosologic position of giant-cell arteritis are also discussed, with regard to its possible allergic character and its relationship to other obliterative arterial disease.

Another case, that of a 55-year-old woman, is considered briefly. She died as a result of small meningeal and intracortical hemorrhages due to a peculiar giant-cell arteriolitis, which is probably closely related to giant-cell arteritis. The authors feel that giant-cell arteritis should be added to the group of vasal diseases that may produce immediate damage to the brain.

AIGNER, Rochester, Minn.

CEREBRAL INFARCTION SECONDARY TO OCCLUSIVE ARTERIAL DISEASE. J. L. CHASON, Radiology 70:811 (June) 1958.

Infarcts of the brain are divided into two pathologic forms: the commoner anemic type, and the less common hemorrhagic type. The only three common causes for areas of infarction in the brain are atherosclerosis, thrombosis, and embolism.

When an anemic infarct is produced, softening and liquefaction of the brain tissue gradually ensue, leading to early and progressive enlargement of the region infarcted. The period of progressive enlargement ends when the rate of removal of the necrotic contents of the infarcted area exceeds the rate of attraction of fluid and reactive cells. This usually occurs toward the end of the third week after infarction. During the period of enlargement of the infarct radiographic signs of an expanding mass lesion may be present, which may lead to the mistaken diagnosis of tumor: The pineal gland may be shifted; pneumoencephalograms may show decrease in size of the adjoining ventricular spaces, or even displacement of the ventricular system. A slight degree of papilledema may be found clinically. After the third week the infarct usually becomes progressively smaller. This leads to enlargement of the adjoining ventricular and subarachnoid spaces. If the lining ependyma of the ventricles does not remain intact in contact with the region of infarction, an acquired porencephalic cyst will develop. Hemorrhagic infarction differs from anemic infarction only by the addition of various degrees of bleeding. Enlargement of the hemorrhagic infarct thus occurs earlier, is of greater degree, and usually persists for a longer time than that in the anemic infarcts. The arterial system distal to the obstructing lesion tends to undergo changes that are damaging to reestablishment of collateral circulation. Passive engorgement of blood vessels occurs and is often followed by necrosis of the blood vessels. Stagnation of blood flow permits organization of platelets and fibrin within the lumen of the vessels and sometimes stimulates hyperplasia of the intima of the vessels. Release of material from the thrombus which causes the main occlusion can produce arterial and capillary emboli distal to the infarct. Distal extension of a thrombus causes another serious threat to availability of the existing collateral channels.

WEILAND, Grove City, Pa.

EXPERIMENTAL RESULTS OBTAINED IN SUBACUTE INCLUSION BODY ENCEPHALITIS OR SUBACUTE SCLEROSING LEUCO-ENCEPHALITIS. S. PELC, J. O. PERIER, and L. QUERSIN-THIRY, Rev. neurol. 98:3, 1958.

Three children, aged about 7 years, developed an illness characterized by intellectual deterioration, followed by myoclonic jerking and progressive paresis, and terminating in a state of decerebrate rigidity. Examination of the brain revealed evidence of inclusion-body encephalitis and widespread demyelination of the central white matter of the cerebrum. The cerebral tissue collected within 20 hours after death was appropriately prepared to remove bacteria. It was then inoculated intracerebrally into mice and rats but did not induce any encephalitis. Material obtained by biopsy of the cerebrum 18 hours before death was also prepared to be bacteria-free and was injected in mice, rats, and two monkeys. The mice and rats were unaffected, but both monkeys developed the encephalitis. Cerebral tissue from the monkeys was then inoculated into three other monkeys, and this inoculation resulted in one of the monkeys developing encephalitis. Efforts to transmit the encephalitis from this last monkey to another group of monkeys failed. Histologic examination of the affected monkeys revealed the most intense encephalitic changes in the inoculated hemisphere, but changes were also present elsewhere in the cerebrum and brain stem. Cells with acidophilic inclusion bodies in the nuclei were encountered, but less frequently than in the original human material. It appeared that the pathogenic agent of this illness could be transmitted to monkeys.

BERLIN, Mount Vernon, N. Y.

Psychiatry and Psychopathology

PSYCHIATRIC SYMPTOMS ASSOCIATED WITH OCCLUSIVE CEREBRAL VASCULAR DISEASE. G. TOURNEY, B. D. COHEN, and J. S. GOTTLIEB, Radiology 70:831 (June) 1958.

Tourney, Cohen, and Gottlieb studied 24 patients suffering from occlusive cerebral vascular disease, which had been demonstrated by cerebral angiograms. An attempt was made to correlate phychiatric and psychological findings with the site and extent of the patient's vascular lesion. Psychiatric symptoms and psychological findings included anxiety, depression, hypochondriasis, impulsivity, delusional content, and many signs of intellectual deficit and deterioration. No relationship was found between the localization of the lesion and the psychiatric

symptoms. There was a possible relationship between age and the degree of intellectual deficit. The gradient of deficiency is sharper in old people with cerebrovascular disease than the normal gradient anticipated with the aging process. However, not enough patients were studied for statistical significance. As has been noted in previous studies of organic brain disease, premorbid personality trends tended to become exaggerated with organic disturbance.

WEILAND, Grove City, Pa.

Meninges and Blood Vessels

LISTERIA MONOCYTOGENES MENINGITIS. C. HOWE and H. SOUTHWORTH, Ann. Int. Med. 48: 1384 (June) 1958.

Howe and Southworth report the case of a 62-year-old woman who had acute onset of lassitude, fatigue, and chills, followed by headache and back pain. Stiff neck then developed. The white blood count was 13,600 per cubic millimeter, with 88 polymophonuclear leukocytes. Spinal puncture revealed 1,120 white blood cells with 90% polymorphonuclear cells. Culture revealed an organism characterized as a diphtheroid, as well as Micrococcus (Gaffkya) tetragenus. These were both considered contaminants. Penicillin, sulfadiazine, and chloramphenicol were given. The patient gradually improved, and treatment was discontinued after the ninth day. On the 21st day the signs and fever recurred, when the diphtheroids were again found. When these proved lethal for mice, it was suggested that the organism be Listeria monocytogenes. The patient was again treated with antibiotics and improved rapidly. Six months later she was in good health.

The organism is a Gram-positive bacillus. It produces beta hemolysis on sheep blood agar and was lethal in adult mice 18 hours after intraperitoneal inoculation. The diphtheroid was considered the causative agent, and the Micrococcus was considered a contaminant. The patient's serum failed to agglutinate the micro-organism even in low dilution.

AIGNER, Rochester, Minn.

A SYSTEMIC ANALYSIS OF INTRACRANIAL ANEURYSMS FROM THE AUTOPSY FILE OF THE PRESBYTERIAN HOSPITAL 1914 TO 1956. E. M. HOUSEPIAN and J. L. POOL, J. Neuropath. & Exper. Neurol. 17:409 (July) 1958.

Housepian and Pool reviewed 113 documented cases of intracranial aneurysm found in 8,762 brains examined from 1914 to 1956. The over-all incidence was 1.3%; 54 were female and 59 were male. The ages varied from 13 to 91, but the lesions occurred most frequently in the third, fourth, and fifth decade of life. In over 3,000 brains examined no cases were found in children from 1 day to 12 years of age. Etiologically, four separate types of intracranial aneurysm are traditionally accepted—mycotic, syphilitic, arteriosclerotic, and congenital. The authors replace the controversial terms arteriosclerotic and congenital with the terms fusiform, saccular, and saccular associated with arteriosclerosis.

Seventeen per cent of the cases showed associated extracranial anomalies, varying from aberrant coronary arteries to an accessory pancreas. Only four intracranial anomalies of the circle of Willis were found in the entire series. There were 99 cases of single and 14 cases of multiple aneurysms. Of the latter group, 70% had two aneurysms. Forty-one per cent were located on some portion of the internal carotid artery. The next most frequent site in the total series was in the middle cerebral artery, 17%; the anterior communicating artery, 11%. Thirteen per cent occurred in the vertebral circulation. Of 71% of the patients death was due to aneurysm—50% initially and 21% subsequently. It was evident that the patients who survived three months from the time of the onset of symptoms had a progressively better chance for long life. Thirty per cent of the patients had hypertension.

According to the figures derived from the analysis, there is a 17% chance that an existing aneurysm will remain asymptomatic, undiscovered, and not responsible for the patient's death. Fatal encephalomalacia or compression of vital structures as a direct consequence of the aneurysm is in store for the 29% of patients whose symptomatic aneurysms do not rupture. If symptoms do develop and there is angiographic demonstration of a single aneurysm, there are a 12% likelihood of a second aneurysm, and an equal probability that it is in the posterior or vertebral circulation.

AIGNER, Rochester, Minn.

ANEURYSM OF THE VEIN OF GALEN. A. HIRANO and R. D. TERRY, J. Neuropath. & Exper. Neurol. 17:424 (July) 1958.

Hirano and Terry report the ninth autopsied case and give a brief summary of previous reports on an aneurysm of the vein of Galen. The case involves a 2½-year-old child with hydrocephalus since the age of 5 months. Postmortem examination revealed a partially thrombosed aneurysm of the vein of Galen, which communicated with the dilated straight sinus and caused hydrocephalus by compressing the aqueduct.

Of the 17 recorded cases reviewed, all showed arteriovenous communications involving the posterior cerebral artery. Arteriography was diagnostic in 10 cases, 8 in carotid and 2 in vertebral injections. Evidence of subarachnoid bleeding was present in six cases.

AIGNER, Rochester, Minn.

Diseases of the Brain

THE NEUROLOGICAL COMPLICATIONS OF MUMPS. R. R. RUSSELL and J. C. DONALD, Brit. M. J. 2:27 (July 5) 1958.

After reviewing previous reports on the neurological complications of mumps, Russell and Donald report a discussion of 18 cases of meningitis and 1 case of encephalitis arising in an epidemic of 287 cases of mumps. Previous reports indicate that meningitis is a not uncommon benign complication, which completely subsides within a few days. Encephalitis is an extremely rare but serious complication, with a mortality rate of about 20%. Most authorities attribute the meningitis to the direct action of the virus. Views on the etiology of the encephalitis have been conflicting. Some attribute it to further extension of the virus from the subarachnoid space into the neuraxis. Others believe it is due to a nonspecific allergic reaction to virus protein.

ECHOLS, New Orleans.

Treatment, Neurosurgery

NEUROSURGICAL ASPECTS OF OCCLUSIVE CEREBRAL VASCULAR DISEASE. J. E. WEBSTER, E. S. GURDJIAN, D. W. LINDNER and W. G. HARDY, Radiology 7:0825 (June) 1958.

Webster, Gurdjian, Lindner, and Hardy have obtained cerebral angiograms on 200 patients admitted with the clinical diagnosis of "stroke" to a cerebral vascular ward. Using the information obtained from these roentgenographic studies plus the information obtained from clinical and neurological examination, they found many different causes for the "strokes" in these 200 patients. Forty-one of the patients had occlusions of the internal carotid artery. Twenty-one of these occlusions were complete, and twenty were partial. There were 15 occlusions of the anterior cerebral artery. The basilar artery was partially occluded in 15 patients and completely occluded in 5. Occlusion of the middle cerebral artery, the one usually suspected in a "stroke," was found in only nine patients. Sixteen patients had brain tumors. Other causes of the "strokes" were hematoma, brain abscess, embolus, cerebral hemorrhage, cerebrovascular insufficiency, aneurysm, and encephalitis.

The authors believe that compression of the contralateral carotid artery in the neck is a valuable and safe test for cerebral vascular insufficiency in the presence of hemiparesis or hemiplegia. In partial or complete contralateral occlusion of the internal carotid artery or the anterior cerebral artery or the basilar artery, syncope will occur in most patients. Syncope does not usually occur in patients with tumors or with occlusions of the middle cerebral artery.

It is worth while to make these diagnostic efforts both to learn about occlusive cerebrovascular disease and to separate vascular disease from other diseases which may simulate it. In the 10% of patients who are found to have a mass lesion instead of vascular disease exploration can be carried out, perhaps with cure. Patients with partial occlusion of the common carotid artery can sometimes be treated by performing an intimectomy at the site of the stenosis.

WEILAND, Grove City, Pa.

Encephalography, Ventriculography and Roentgenography

A SUGGESTION FOR DIMINISHING THE AMOUNT OF GAS INTRODUCED INTO THE SUBDURAL SPACE DURING LUMBAR PNEUMOENCEPHALOGRAPHY. B. S. EPSTEIN and J. A. EPSTEIN, Am. J. Roentgenol. 80:95 (July) 1958.

Epstein and Epstein perform a lumbar puncture in the fourth or fifth lumbar interspace. They make scout roentgenograms after the instillation of 10 to 20 cc. of gas. If the subtentorial

or subdural space is visualized, the needle is withdrawn immediately and reinserted at least two interspaces higher. When a free flow of cerebrospinal fluid is obtained, the needle is pushed in from 3 to 5 mm. deeper, and if a continuous free flow is obtained, 10 to 20 cc. more of gas is instilled. Further scout roentgenograms are made. The examination is continued if air is found in the ventricular system.

If a diagnostic lumbar puncture has been performed within a week preceding the pneumoencephalogram, the second puncture is made two interspaces above the original site. It is preferable to combine a diagnostic lumbar puncture with a pneumoencephalogram when possible in order to avoid repeating the lumbar puncture.

WEILAND, Grove City, Pa.

LATERAL MIDLINE LAMINAGRAPHY IN ENCEPHALOGRAPHY AND VENTRICULOGRAPHY. F. C. SHIPPS and J. RAAF, Am. J. Roentgenol. 80:98 (July) 1958.

Shipps and Raaf have been impressed with the consistent improvement in detail in the midline structures when laminagraphy has been used with the patient in the lateral position during pneumoencephalography. They have made it a routine to take a lateral laminagram in all cases in which pneumoencephalography or ventriculography is performed. Since adding lateral laminagraphy to the routine air studies, the fourth ventricle has been demonstrated in all but 2 of 22 normal cases. The impression has been gained that if there is a moderate amount of ventricular filling and the fourth ventricle is not shown by laminagraphy, a cerebellar or brain stem lesion may be suspected. Visualization of the third ventricle, the aqueduct of Sylvius, and the fourth ventricle has been improved greatly over that in the use of routine lateral views. Shipps and Raaf point out that positioning of the head in the lateral position with brow and vertex a little closer to the table top than the chin and occiput results in a better laminagram of the third ventricle than a film taken with precise standard lateral positioning.

WEILAND, Grove City, Pa.

THE ANGIOGRAPHIC EVALUATION OF CEREBRAL ATHEROSCLEROSIS. M. TATELMAN, Radiology 70:801 (June) 1958.

Tatelman reports on a series of 250 consecutive patients admitted to the cerebral vascular service of a Detroit hospital with the clinical diagnosis of "stroke" or "cerebral vascular accident." Each of these 250 patients was studied by carotid or vertebral angiography or both. In the earlier cases only the side implicated by clinical and neurological findings was examined. Later in the series all cases were studied by bilateral carotid angiography, and some had vertebral angiography performed also. One death was reported in the series. It was felt that the procedure was relatively safe because many of the patients were in very poor clinical condition, yet survived the procedures.

Cerebral atherosclerosis and its effects, detectable in the angiograms, were considered to be the cause of the patient's symptoms in 58% of the cases studied. Complete occlusion of the internal carotid artery accounted for 10.5% of the cases in the series. Partial occlusion of the interal carotid artery was found and considered to be the cause of "stroke" symptoms in 10% of the cases. Most of the occlusions and all the partial occlusions occurred immediately above the origin of the internal carotid artery in the neck. Occlusion of the middle cerebral artery accounted for only 4.5% of the 250 patients; most of these occlusions occurred close to the origin of the artery. Failure of filling of one anterior cerebral artery was found in 7.5% of the series. Often the anterior cerebral artery which fails to fill will be filled when the contralateral carotid artery is injected. This has led some physicians to the opinion that in many cases nonfilling of the anterior cerebral artery has no pathologic significance. Tatelman feels that many, if not all, of his cases of nonfilling of the anterior cerebral artery were caused by atherosclerosis. His patients showed symptoms of a cerebral abnormality which could not be explained by any other finding; in most cases characteristic convulsive movements and syncope were produced by digital compression of the contralateral carotid artery; pneumoencephalography showed localized atrophy of the frontal lobe in some cases; the involved anterior cerebral artery could not be filled on repeated injection, and anatomic studies have shown that sigificant variations in size of the anterior cerebral artery are very uncommon.

Five patients in the series were found to have occlusion of the vertebral-basilar system, accounting for 2.5% of the total "strokes." However, vertebral angiography was not frequently performed in this series. Minor changes of atherosclerosis can be found frequently in the cerebral arteries if looked for. Signs of atherosclerosis are irregularity in the lumen of the artery, narrowing, dilatation, and abnormal tortuosity of the artery. Straightening and elongation of arteries also sometimes indicate atherosclerosis. Dilatation and elongation of the basilar artery are a rather striking atherosclerotic change.

WEILAND, Grove City, Pa.

Books

Contribuicão ao estudo clínico da epilepsia temporal: Manifestacões clínicas em 1000 pacientes portadores de foco temporal no electroencefalograma. By Jorge Armbrust Figueiredo. Price, not given. Pp. 285, with 45 tables, 43 charts, and 393 references. Escolas Profissionais Salesianas, São Paulo, 1958.

This is a detailed clinical study of 1,000 patients with electroencephalographic abnormalities limited to the temporal lobes. The patients were divided into groups according to the locus of the disturbance: unilateral *vs.* bilateral, anterior *vs.* posterior, superficial *vs.* deep, right *vs.* left. The symptomatology was then codified four ways, according to subjective *vs.* objective and paroxysmal *vs.* interval manifestations. An elaborate subdivision into vegetative, sensorial, and psychic phenomena was then undertaken. Excluded from consideration were patients who manifested signs of cerebral damage by roentgenograms and often by pneumoencephalograms and angiograms. The study is therefore the "temporal-spike syndrome."

Paroxysmal disturbances of consciousness occurred in 93%, automatisms in 63%, objective psychic manifestations in 62%, subjective in 58%, sensorial in 45%, and interval objective and subjective manifestations in 35% and 28%, respectively.

Analyzing the patients with unilateral *vs.* bilateral foci, vegetative manifestations were common to both, while sensorial phenomena were predominantly unilateral and psychic were mostly bilateral. Automatisms, facial, adversive, aphasic seizures indicated unilateral foci, while simple absences and generalized seizures occurred predominantly in bilateral cases. Interval subjective and objective phenomena occurred principally in bilateral projections.

Sensorial phenomena occurred more frequently in connection with superficial foci, whereas psychic (emotional and intellectual) disturbances were commoner with deep foci. This was true both of the paroxysmal and of the interictal disturbances.

There was rather marked predominance of sensorial and psychic manifestations in patients with left-sided spikes, while vegetative crises showed no preference.

Visual, auditory, and common sensory experiences occurred in patients with involvement of the posterior portions, while olfactory, vestibular, and gustatory experiences pointed to the anterior portions. Vegetative phenomena predominated in anterior foci. All the psychic phenomena except the déjà vu pointed to the anterior portion. Interval objective aberrations appeared with greater frequency in patients with anterior foci, though the subjective interval manifestations had no such specific localizations.

A summarizing table on pages 246-247 is useful, since it contains only a few words that would require the reader to consult a dictionary.

The author makes good use of the world literature on epilepsy, particularly that pertaining to the temporal lobe, the psychomotor seizures, and the epileptic equivalent, and uses the various terms with easy familiarity. Dickens and Dostoevski are included in the bibliography. The writing is clear and straightforward, and the Portuguese language is easier to follow than either French or Spanish.

The one criticism of this clinical study is that insufficient attention has been paid to the handedness of the patient. Some of the tables and charts might present even more striking differences had the author used dominant *vs.* nondominant temporal lobe rather than right *vs.* left. He does mention that aphasic attacks occurred in eight patients with spikes in the right temporal lobe, six of whom were left-handed. Only rage and euphoria, in comparison with ictal aphasia, showed equally significant lateralization to the left hemisphere.

It would appear unlikely that any epileptic phenomena would hitherto have escaped description in the literature, yet Figueiredo, using the fine-mesh net of clinical investigation, found 30 to 40 patients who experienced vestibular and auditory sensations between attacks. Mostly these were prolonged aftermaths of seizures, analogous to Todd's paralysis. Ten patients experienced paresthesias and two anesthesia in the intervals between attacks. There seemed to be no significant correlation with the location of the electroencephalographic foci. The author states that these phenomena have not been reported in the literature that he has consulted, covering more than 5,000 cases.

In summary, Figueiredo has examined 16,000 tracings, selected 1,000 of isolated temporal spikes and made a scholarly study of the clinical manifestations, correlating the electrographic with the clinical in a very useful manner.

WALTER FREEMAN, M.D.

A Textbook of Neurology. Second Edition. By H. Houston Merritt, M.D. Price not given. Pp. 780, with 182 illustrations. Lea & Febiger, 600 S. Washington Sq., Philadelphia 6, 1959.

The appearance of the second edition of this Textbook of Neurology just four years after the first is testimony of its excellence and of the rapid advances in clinical therapeutic neurology. Dr. Merritt again, as in his first edition, presents us with a concise, clear account of the various neurological syndromes and brings us up to date on pathophysiology and treatment. He has brought his text up to date on the fundamental discoveries in metabolic and viral diseases of the nervous system. Advances in the treatment of cerebrovascular diseases are included, but he has introduced a note of caution concerning anticoagulant therapy of cerebrovascular disease.

This new edition is well illustrated and punctuated with a series of excellent tables. The author's style is notably direct and clear.

This text is recommended as an outstanding addition to the neurological literature for students and physicians alike.

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*Livingston, S., and Petersen, D.: New England J. Med. 254:327 (Feb. 16) 1956.

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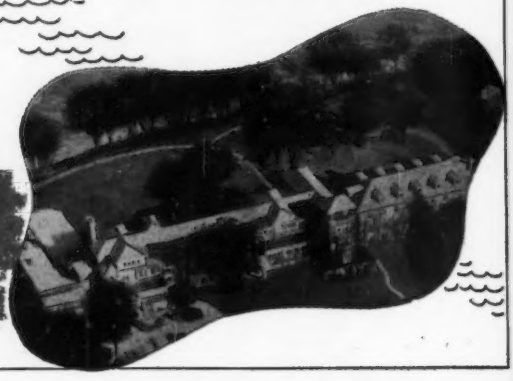

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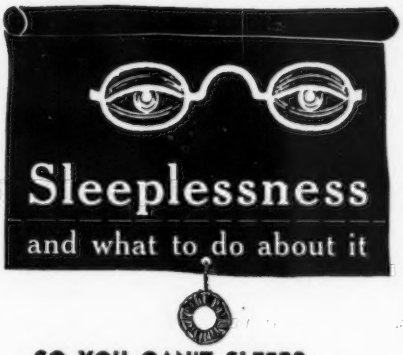

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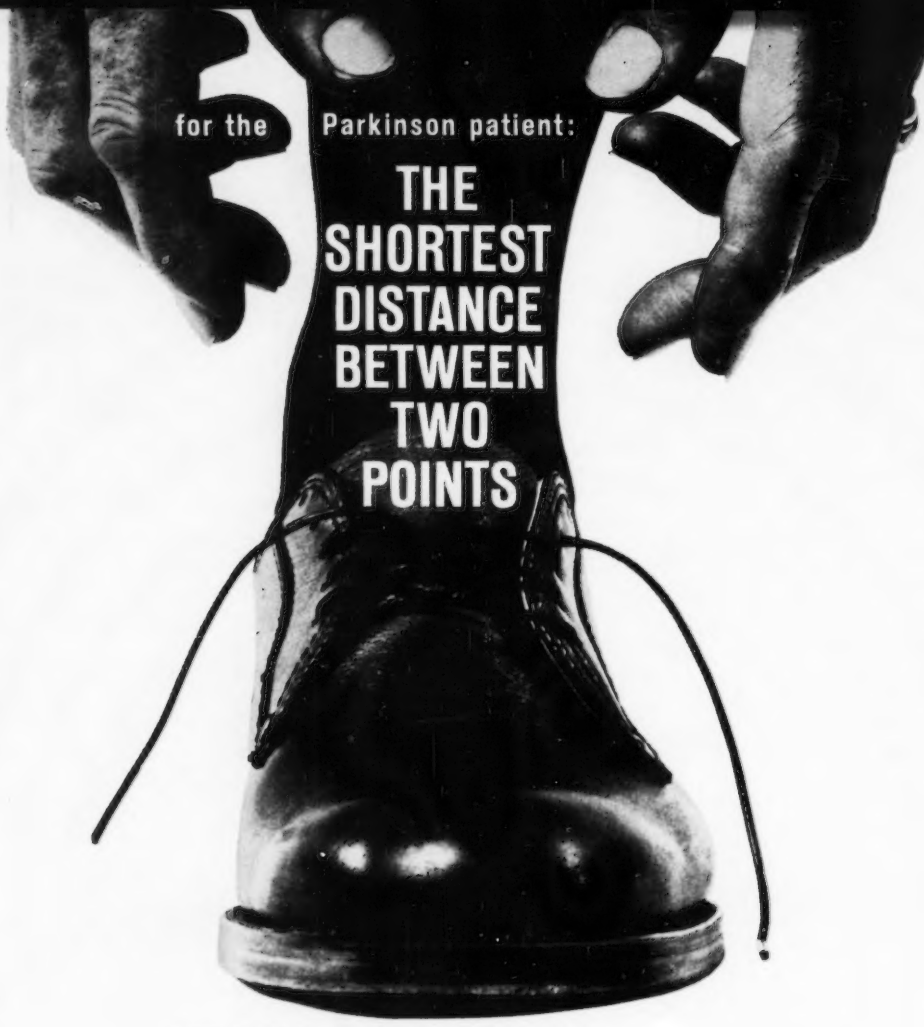

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